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Chest Pain in Association with Pulmonary Hypertension

Its Similarity to the Pain of Coronary Disease

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This communication deals with a type of chest pain which is not uncommon, and which is likely to lead to an erroneous diagnosis of coronary arterial disease. The term "hypercyanotic angina," which has been applied to the syndrome in the past, is unfortunate because many of the patients are not cyanotic, and further because the physiologic mechanism of the pain, while still obscure, appears to be different from that of the pain of angina pectoris. In the patients we have observed, the one constant feature other than pain has been clinical evidence of increased pressure in the pulmonary vascular circuit. Hence, the term "pulmonary hypertensive pain" is employed, but with the reservation that more complete knowledge of the exact pathogenesis may make a different name desirable.

PULMONARY hypertensive pain may resemble angina pectoris not only as regards location, radiation, intensity, and quality of the discomfort, but also as regards the tendency to be initiated by physical exertion. In some patients the pain may be associated with outspoken electrocardiographic changes. (See figures 1 and 2.) Therefore, the diagnosis of myocardial infarction is likely to be made. The differentiation, while occasionally almost impossible, can usually be made with accuracy if one is familiar with the various clinical features of the syndrome.

In 1942 Burgess and Ellis wrote an excellent review article on chest pain in patients with mitral stenosis.[1] They referred to Nothnagel's publication[2] on the same subject, and summarized the more important papers dealing with angina-like pain in various disorders of the pulmonary vessels. Thus Vaquez and Giroux[3] described the clinical findings of *angina pulmonaire hypercyanotique* associated with pulmonary arteriosclerosis. Posselt[4] cited chest pain (*dysphagia intermittens angiosclerotica pneumonalis*) as one of the criteria for the diagnosis of pulmonary arteriosclerosis. Frugoni[5] contrasted *dolor pallidus* of angina brought on by effort with *dolor caeruleus* seen in patients with pulmonary arterial disease. Other publications dealing with chest pain in relation to pulmonary arteriosclerosis include those of Arrillaga,[6] Engelen,[7] Brenner,[8] and Brill and Krygier.[9]

Pain resembling that of angina pectoris in patients with mitral stenosis was clearly described by Nothnagel.[2] Sternberg[10] reported autopsy findings of a patient with mitral stenosis who before death experienced severe pain of this type. The coronary arteries were described as being thin and widely patent. Parker and Weiss[11] stated that pain and cyanosis were frequent symptoms of mitral stenosis when there were secondary pulmonary changes, and that these same symptoms were usually absent when such secondary changes were lacking.

In recent years there has been much interest in the subjects of anticoagulant therapy and thromboembolic disease. Compared to the numerous papers dealing with the electrocardiographic changes associated with pulmonary embolism, there have been relatively few reports in which the pain produced by the disorder has been carefully described. McGinn and White[12] reported that most patients with pulmonary embolism complained initially of dyspnea and substernal oppression. They also re-

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ferred to another type of pain which appeared later, and was always associated with pleural involvement. Fenn,[13] and Murnaghan, McGinn and White,[14] in describing the typical picture of pulmonary embolism, pointed out the difficulty that is sometimes encountered in the differentiation of the pain of pulmonary embolism and that of myocardial infarction, the typical picture of both being "sudden severe pain in the chest associated with circulatory collapse." They indicated that the typical pleural pain usually did not appear until some hours later, when a pleural friction rub was often present. This pleural pain may be located in either side of the chest, in the back, or in the shoulder, if the diphragmatic portion of the pleura is involved. There are many other reports in the literature which describe pain associated with pulmonary embolism, but there are few which distinguish clearly the two different types of pain that were delineated by the authors cited above.

It should be re-emphasized that pulmonary embolism and pulmonary infarction are not synonymous terms. Pulmonary embolism produces pain resembling that of myocardial infarction, while pulmonary infarction produces pain resembling that of acute infectious pleuritis. When, as is often the case, embolism is not followed by infarction, only the first type of pain occurs. The pain produced by pulmonary embolism appears to be identical in character and mechanism with that caused by other disorders which cause elevation of pressure in the pulmonary artery. This point is illustrated by the case histories to be presented.

Illustrative Cases

Most of the patients whom we have thought to be suffering from pain as the result of pulmonary hypertension have had either (1) lesions of the mitral valve; (2) certain congenital anomalies of the heart; (3) primary diffuse disorders of the lungs, especially asthma and emphysema; or (4) disorders of the pulmonary artery and, more particularly, embolism. In many instances there has been no proof of the diagnosis, and the decision that the pain was induced by pulmonary hypertension rather than by coronary disease has rested on opinion rather than on conclusive evidence. The cases cited below were selected for presentation either because autopsy confirmation was available, or because the clinical evidence seemed reasonably conclusive. In order to conserve space, only the most pertinent data are presented in the following case reports.

Case 1. W. A., a 77 year old white man, was admitted to the hospital with the following history: One week before admission, while sitting in a chair at about 10:00 P.M., he noted severe precordial pain, became dyspneic and cyanotic, and in a few seconds slumped from the chair unconscious. His breathing was stertorous and cyanosis was marked. The following morning he could be aroused but was irrational, and continued so until admission.

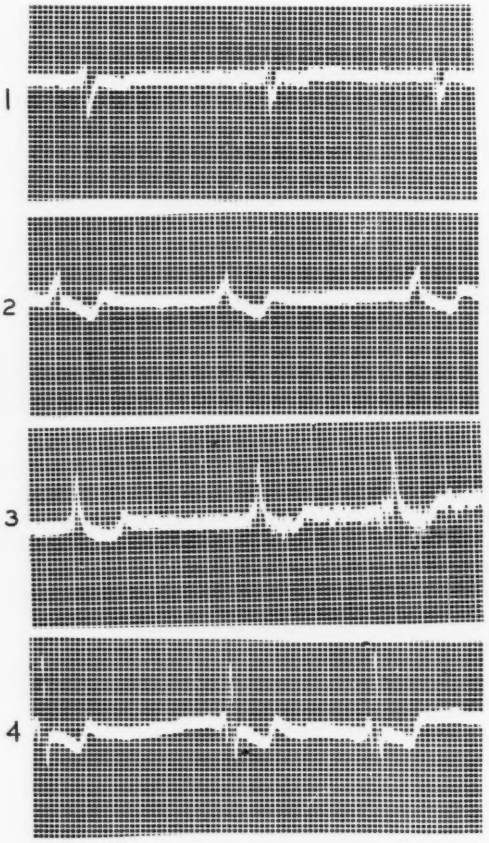

Fig. 1. The record was interpreted as being compatible with myocardial infarction. Postmortem examination proved this to be untrue. Instead, there was marked dilatation of the right side of the heart and a striking dilatation of the pulmonary artery and its branches.

He had complained of precordial pain on exertion, and occasionally at rest, for the year preceding the present episode.

Physical examination revealed a senile, irrational, cyanotic white man with Cheyne-Stokes respiration. The lungs were clear except for fine moist rales at both bases, posteriorly. The blood pressure was 150/80; the pulse was grossly irregular, with a precordial rate of 82 and a radial rate of 70. Precordial

pulsations were prominent, extending from the third to the sixth intercostal space. The area of cardiac dullness extended from the anterior axillary line to the right border of the sternum. The heart sounds were loud. A loud, harsh murmur was heard throughout systole. It was loudest over the apex but was heard with diminishing intensity over the entire precordium, and radiated into the left axilla. During the phases of apnea, a diastolic murmur could be heard in the third and fourth intercostal spaces in the midclavicular line. The quality of this murmur was midway between the rumbling diastolic murmur of mitral stenosis and the blowing diastolic murmur

FIG. 2. In the center of the photograph the markedly dilated pulmonary artery is held open by a glass rod.

of aortic insufficiency. The liver was palpated 3 cm. below the right costal margin. X-ray films revealed a marked prominence in the area of the pulmonary segment which, on fluoroscopy, pulsated synchronously with the heart beat. Marked dilatation of the major branches of the pulmonary arteries was seen. Electrocardiograms (fig. 1) were interpreted as being indicative of definite myocardial damage which was thought to be compatible with myocardial infarction.

He was placed in an oxygen tent, given digitalis, and put on a salt-free diet. He gradually improved until his death, which occurred suddenly about two months following admission to the hospital. Terminally, he became markedly dyspneic and cyanotic. The radial pulses were not palpable. Death occurred less than five minutes after the onset of this final seizure.

Postmortem findings revealed a markedly dilated and moderately hypertrophied right ventricle, with striking dilatation of the pulmonary artery (fig. 2) and of its main branches extending into the lesser divisions to the periphery of each lung. There was only moderate sclerosis of the pulmonary vessels. The right pulmonary vein entered the right auricle. The commissures of the pulmonary valve were separated and the intervening space was occupied by a thin fenestrated membrane. There was an interauricular septal defect 2 cm. in diameter, located in the upper posterior portion of the septum. There was one small calcified plaque in the posterior leaflet of the mitral valve. The coronary vessels were patent throughout. There was no scarring of the myocardium.

Comment. Although the history was incomplete, there was a story of recurrent attacks of precordial pain often brought on by effort, and occasionally occurring at rest. A more severe and prolonged attack was accompanied by cyanosis, dyspnea, and loss of consciousness. The electrocardiogram was interpreted as being compatible with the diagnosis of myocardial infarction. Thus the clinical picture resembled that of coronary disease, but the necropsy revealed no evidence either of coronary disease or of myocardial infarction. The findings were those of congenital defects of the pulmonary veins, interauricular septum, and pulmonary valve, leading to enlargement of the right ventricle and pulmonary vessels. Presumably, the systolic pressure was markedly elevated in the pulmonary artery.

Case 2. A 72 year old white man for four years had had severe paroxysms of bronchial asthma. Shortly after the beginning of the asthma he developed chest pain. This was substernal in location, aching and occasionally cramping in character, and lasted from a few minutes to several hours. The pain came only with severe asthmatic paroxysms, and invariably lasted until relief from the asthmatic attack. Nitroglycerin produced an incomplete relief from pain only to the extent that it relieved the dyspnea.

Physical examination made during an asthmatic attack revealed the patient to be lying flat in bed with inspiratory retraction of the supraclavicular and suprasternal areas with prolonged expiration. Eye grounds revealed grade I arteriosclerotic changes. There was a marked increase in the anteroposterior diameter of the chest, so that it was typically barrel-shaped. The chest was hyperresonant

throughout. During a paroxysm, voice sounds were obscured completely by high-pitched sibilant rales heard all over the chest. Blood pressure was 150/100; pulse 76, with frequent premature beats. The point of maximum impulse could not be felt and percussion was unsatisfactory because of emphysema. The heart sounds were faint and almost replaced by a moderately loud, harsh systolic murmur. The murmur was loudest at the apex and was transmitted, but was also heard over the aortic area where it was of slightly lower pitch. The asthma was helped by adrenaline when mild, and relieved by aminophylline when severe. When the dyspnea improved the pain, likewise, subsided.

Electrocardiogram revealed multiple premature beats of ventricular origin, left axis deviation, inversion of T waves in leads II and III, and deep QS complexes in precordial leads I, II, and IV. Chest x-ray films revealed fibrotic changes throughout both lung fields.

Death occurred after 15 months in the hospital. Necropsy revealed marked dilatation and hypertrophy of the right auricle and right ventricle, and dilatation of the pulmonary conus. There was minimal cirrhosis of the liver, and chronic cholecystitis without stones. There were no abnormalities of the coronary arteries, and the myocardium was normal except for hypertrophy and dilatation, as noted above.

Comment. This patient was considered to have had an old myocardial infarction on the basis of the history and the electrocardiogram. However, the autopsy revealed no evidence of infarction or coronary artery disease. The relationship of the pain to the dyspnea and the response to drugs (little or no relief from nitroglycerin; marked benefit from adrenaline and aminophylline) were typical of the pulmonary hypertensive pain associated with bronchial asthma.

Case 3. N. H., a 77 year old Negro man, entered the hospital for the first time on August 8, 1948 because of a slow urinary stream, dribbling of urine for one week, and retention of urine for 48 hours.

Physical examination was negative except for a very large prostate gland. On August 9, a prostatectomy was done, with removal of 78 Gm. of prostatic tissue. The patient remained in bed until August 12, at which time he began to be up and about. On August 18, at 7:30 A.M., the patient collapsed in the bathroom. He was found on the floor unconscious and dyspneic, and the pulse was absent. At 8:00 A.M. he was breathing rapidly and shallowly. The pulse was weak and irregular, with a rate of 100. The blood pressure was 100/60. The patient was covered with sweat. The lungs were clear. Cardiac examination revealed the second pulmonic to be much louder than the second aortic sound.

A short time later the patient said that he was experiencing a constant, pressing, severe substernal pain that radiated to his left shoulder and left arm. The pain persisted for about three hours. Morphine, oxygen, papaverine, heparin, and dicumarol were administered.

Electrocardiographic changes in the next 24 hours were interpreted as being compatible with an acute subendocardial anteroseptal myocardial infarction. The patient improved and it was thought that he was progressing favorably when on August 21, three days later, he was found dead.

Necropsy revealed thrombophlebitis of the right femoral vein and massive pulmonary embolism. There was benign prostatic hypertrophy, cortical necrosis and arteriolar nephrosclerosis. The coronary vessels were widely patent and no abnormalities were observed. There was no evidence of myocardial infarction.

Comment. The clinical findings were compatible with myocardial infarction and the electrocardiogram was so interpreted. Necropsy revealed pulmonary embolism without evidence of disturbance in the coronary circulation or myocardium. This patient illustrates the difficulty in differentiating pain associated with pulmonary hypertension from that associated with coronary disease.

Case 4. O. H. F., a 48 year old white man, was admitted to the hospital on May 27, 1947, complaining chiefly of shortness of breath of five years' duration, and pain in the chest of four years' duration. The patient had developed a chronic cough 10 years previously.

In 1942 he developed pain in the right parasternal area. (He had known since 1918 that his heart was on the right side.) The pain was described as having a sharp, tearing, and squeezing quality. It usually followed several hours of exertion, was associated with severe dyspnea, and usually persisted for one to two hours, but occasionally lasted several days. It was definitely aggravated by deep breathing, being especially worse on inspiration. Nitroglycerin produced no relief from the pain. As his dyspnea improved, the pain always diminished in intensity. The pain was nonradiating.

Physical findings revealed a 48 year old man lying flat in bed, in no distress. Optic fundi showed only slight narrowing of the vessels, with no arteriovenous nicking. The chest was full but not barrel-shaped. The right hemithorax was considerably fuller than the left, measuring 5 cm. greater. The lung fields were clear. The vital capacity was 4 liters. The blood pressure was 162/92. Examination revealed the heart

to be more on the right side than on the left. No other abnormalities were noted.

X-ray study revealed the heart to be mainly on the right side. The vessels occupied the position of a normal left-sided heart. There was also a bilateral emphysema, mainly in the lower lobes. The apical pleura was thickened bilaterally.

Angiocardiograms indicated that the chambers of the heart were in the positions which they would occupy if a normal left-sided heart had been pulled over into the right hemithorax mechanically. Lipiodol bronchograms showed no evidence of bronchial dilatation. Electrocardiogram revealed inverted T waves in lead I.

Comment. Aside from emphysema, this patient had displacement and rotation of the heart due to an unknown cause. It seems probable that these conditions were capable of elevating the pressure in the pulmonary artery. The similarities and differences between the pain of this patient and that in angina pectoris are noteworthy.

Case 5. L. B. H., a white woman aged 77, complained of precordial and substernal aching and tightness for 18 years. This was at first noted only on climbing hills, and would disappear quickly when resting.

She was first examined when she was 52 years of age. At that time there were no complaints other than chronic cough. She had no pain or dyspnea, although she was leading an unusually active vigorous life, including long walks up and down steep hills. At the age of 30 she had had an acute attack of polyarthritis with fever. Examination at that time revealed questionable slight cardiac enlargement and a moderately loud (grade III) apical systolic murmur, heard well out into the axilla. Electrocardiograms displayed no abnormality. The pulmonic second sound was exaggerated.

At age 58 she began to note precordial and substernal aching and tightness. This occurred at first only when she would climb steep hills, and would disappear within two or three minutes when she would stand still. Physical examination was essentially unchanged except that the previously normal blood pressure was now slightly elevated (165/102). The electrocardiogram displayed a tendency toward right axis deviation when compared with the record taken six years previously. X-ray study revealed no significant change other than minimal enlargement and a "mitral shape." During the subsequent 18 years, the exertional pain remained essentially unchanged but occurred less frequently as the degree of activity was gradually decreased as the result of advancing age. The patient gradually noted that the pain would occur when at rest, and more readily in the recumbent position. Anxiety and emotional stress tended to induce it, and the discomfort, while not severe, would last for hours. It was also noted that the distress might endure for several days when acute exacerbations of the chronic bronchitis occurred. Nitroglycerin was taken on numerous occasions, the effects of which were uncertain. At times the pain was unaffected. On other occasions it seemed to disappear more rapidly with than without the drug. The dramatic response that commonly occurs in patients with angina pectoris was not observed. During the entire 25 year period, numerous electrocardiograms were taken. None showed evidence of myocardial ischemia. The systolic murmur gradually became somewhat fainter, and an apical diastolic rumble appeared. At age 77 auricular fibrillation and congestive failure first appeared. Prompt improvement followed digitalization.

Comment. The pain was at first interpreted as angina pectoris. With the passing of years this diagnosis became progressively more untenable, and it now appears altogether likely that pulmonary hypertension, secondary to disease of the mitral valve, was the underlying mechanism. It is noteworthy that chronic nonproductive cough was the most conspicuous symptom.

Case 6. P. W., a 67 year old white man, a construction engineer, was seen in 1951 because of a severe upper respiratory infection and because of being awakened at night "fighting for breath."

Since the age of 21 this patient had been constantly exposed to dust in his occupation.

In 1940 he had an episode of swelling of the feet and ankles which was relieved by some large tablets. It was about this time that he began to notice that less effort than usual made him short of breath.

In 1945, having contracted an upper respiratory infection, the patient noticed an episode of squeezing substernal discomfort associated with marked dyspnea while climbing stairs. The dyspnea and the squeezing discomfort were both relieved after a few minutes of rest. The substernal oppression did not radiate and its intensity was directly proportional to the dyspnea. The patient saw his physician and was hospitalized; he was found to have fairly marked pulmonary fibrosis and emphysema, and mild hypertension.

More recently he had noticed on several occasions, a substernal squeezing discomfort and dyspnea on exertion, and both had always been relieved by rest. Both of these symptoms were exaggerated with episodes of upper respiratory infection. He had been awakened at night on several occasions very short of breath, with a feeling that death was imminent. This would necessitate his getting out of bed, going to a window, and being up most of the

rest of the night. He was finally digitalized and enjoyed marked improvement in symptoms.

The present episode followed a week without digitalis, plus the fact that the patient had contracted an upper respiratory infection which had become quite severe.

Physical examination revealed the patient to be quite dyspneic, very nervous, and drenched with sweat. His blood pressure was 190/120, pulse 120, respirations 32 and temperature 102.6 F. The fundi revealed grade II retinopathy. The neck veins were distended. The chest was increased markedly in its anteroposterior diameter. There was a marked right kyphoscoliosis with a typical pigeon-breast shape anteriorly. Dullness was noted posteriorly on both sides extending from the bases upward to the inferior angle of the scapulae. There was hyperresonance to percussion over the entire anterior chest. Bubbling rales were present at both bases, posteriorly. There were fine crackling moist rales and increased breath sounds in the region of the right middle lobe.

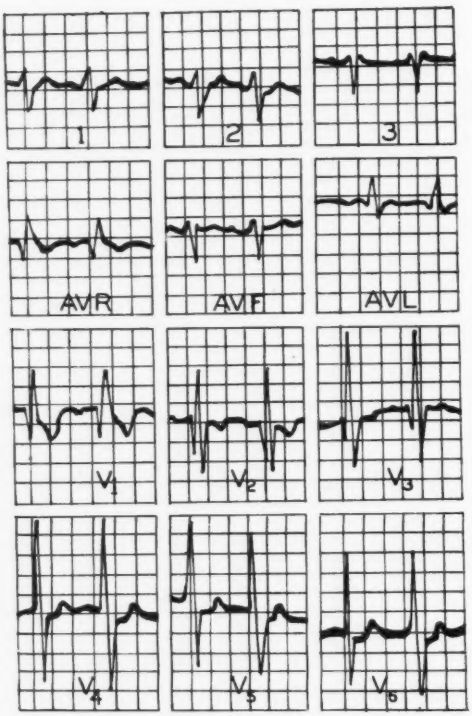

FIG. 3. The record is interpreted as pointing toward hypertrophy of both left and right ventricles. There is also an intraventricular conduction defect. It did not change after exercise sufficient to produce this patient's pain. A record identical with this was obtained five and 10 minutes after nitroglycerin. Nitroglycerin did not prevent the patient's pain nor did it increase his exercise tolerance.

The point of maximum cardiac impulse was both thrusting and diffuse, being most prominent in the fifth left intercostal space in the midclavicular line. It was easily seen and felt in the fifth left intercostal space all the way to the sternum. The right border of cardiac dullness was thought to extend 2 to 3 cm. to the right of the sternum. There was a faint apical systolic murmur and a well marked protodiastolic gallop which changed to a double gallop with inspiration. The liver was palpable 2 fingerbreadths below the right costal margin, and was smooth and nontender. Minimal pitting pretibial edema was present. Peripheral pulses were equal and easily palpable.

The patient was digitalized, given aminophylline suppositories, 0.5 Gm. every six hours, and 300,000 units of penicillin every 24 hours for three days. The improvement was uneventful.

Electrocardiogram (fig. 3) revealed evidence of both right and left ventricular hypertrophy and intraventricular block. Exercise to the point of severe dyspnea and substernal discomfort did not change the appearance of the electrocardiogram. Nitroglycerin did not change the electrocardiogram and did not increase exercise tolerance.

The impression was right middle lobe pneumonia superimposed upon chronic pulmonary fibrosis and emphysema, with hypertension and mild acute pulmonary edema on an already existing chronic cor pulmonale. The substernal pain was thought to be due to pulmonary hypertension with distention of the pulmonary artery.

Comment. This patient had the typical story of pain brought on by exertion and relieved in a few minutes by rest. This story and the electrocardiographic findings could very easily be interpreted as being due to coronary artery disease. However, the set-up of chronic pulmonary disease with substernal distress related so closely to the episodes of dyspnea, the evidence of right ventricular enlargement with cor pulmonale, and the failure of nitroglycerin to have a beneficial effect, would lend support to the diagnosis of pain due to pulmonary hypertension.

DISCUSSION

It is apparent, from the foregoing case histories, that patients with pulmonary hypertension may have pain which is very similar to that produced by disease of the coronary arteries. In so far as location, radiation, qual-

ity, and intensity of the pain are concerned, the two types of pain seem to be identical. There are additional features of the syndrome which enhance the difficulty of differentiating these disorders. Thus some of the patients with pulmonary hypertensive pain (for example, cases 5 and 6) complain of pain brought on by physical exertion, and relieved within a few minutes by rest. Other patients have prolonged bouts of pain enduring for several hours or days, and associated with electrocardiographic changes (cases 1, 2, and 4). It is not surprising that the mistaken diagnosis of coronary arteriosclerosis is usually made in these patients. We, ourselves, have repeatedly made this error, and have treated a number of these patients for several years for supposed diseases of the coronary arteries. Further experience has convinced us that the differentiation, while often difficult and occasionally impossible, can usually be made with accuracy if one is aware of the various clinical features of the syndrome of pulmonary hypertensive pain.

The most important clue to the diagnosis comes from the recognition of the existence of a condition capable of causing pulmonary hypertension, and the realization that such disorders may produce a type of chest pain which mimics closely that due to coronary disease. The most common underlying disorders are: (1) lesions of the mitral valve, usually stenotic, but occasionally regurgitant; (2) primary diffuse disorders of the lungs, especially asthma, emphysema, and bronchiectasis; (3) disorders of the pulmonary arteries, of which embolism is the most frequent; and (4) those congenital malformations of the heart which lead to elevation of pressure in the pulmonary artery. In the latter connection, it is of interest to note that, as would be expected because of pulmonary stenosis and actually a low pulmonary arterial pressure, this pain has not been noted in subjects with the tetralogy of Fallot. On the other hand, it has been repeatedly encountered in patients with auricular septal defects, the Eisenmenger complex, and patent ductus arteriosus.

Not all patients with these several disorders complain of pain. On the contrary, it is absent in the majority of instances. It is, likewise, rarely (if ever) encountered in patients with pulmonary hypertension secondary to left ventricular failure. Whether its absence or presence is dependent on the degree of pulmonary hypertension, or on other factors, is uncertain at present. The important point in diagnosis is the realization that any disorder which is capable of causing pulmonary hypertension *may* produce pain and to demand unequivocal evidence before considering such a patient as having coronary disease.

Aside from objective clinical and roentgenologic evidence of the presence of an underlying disease process which is capable of causing elevation of the pulmonary pressure, there are certain other features which serve as guides in differentiating the pain associated with pulmonary hypertension from that accompanying coronary disease. These are:

1. *A history of long-standing cough.* This is present in many of the patients, but by no means all of them.

2. *Cyanosis,* either persistent or intermittent, and usually present during the episodes of pain. Since patients with angina pectoris or myocardial infarction usually exhibit either pallor or no change in color during the episodes of pain, the presence of cyanosis is of diagnostic value. Unfortunately, cyanosis is not always present during the episodes of pulmonary hypertensive pain.

3. *Association of the pain with dyspnea.* This is a frequent but not a constant feature. Many patients with coronary disease also have dyspnea when they have pain. Most do not, however. It is interesting to note what Heberden said in his description of angina pectoris. "In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different."[15] The presence of typical asthmatic wheezing in a patient with chest pain is a diagnostic clue, provided one can be sure that the underlying disorder is bronchial rather than cardiac asthma.

The dyspnea occurring in patients with pulmonary hypertensive pain is usually of the pulmonary rather than the cardiac type. For

dyspnea of given severity, the vital capacity is likely to be more markedly decreased in the pulmonary than in the cardiac type. Furthermore, the circulation time through the lungs is often normal or only slightly prolonged, except when lesions of the mitral valve are responsible for the pulmonary hypertension.

4. *The presence of pain on breathing.* This is very unusual in patients with angina pectoris,[16] but is not rare in the presence of myocardial infarction, and particularly when there is an associated pericarditis. As has already been emphasized, those patients with pulmonary embolism who develop infarction of the lung usually have a second type of chest pain. This is of pleural origin, with typical respiratory aggravation. Unlike the pain of pulmonary embolism, which is usually situated in the substernal, precordial, or arm areas, the pain of pleuritis is likely to be maximal in the lateral or posterior areas of the chest. Aside from pulmonary embolism, many of the various other conditions which cause pulmonary hypertension are accompanied by recurrent attacks of pleuritis. Thus the presence of two different types of chest pain, one of which is markedly aggravated by breathing, constitutes evidence against coronary disease and in favor of pulmonary hypertension.

Aside from the respiratory aggravation associated with the typical pleural pain, there is another feature which has been observed in some of our patients. This consists in a slight inspiratory increment in the pulmonary hypertensive pain itself. This is presumably due to the increased flow of blood into the chest during inspiration, and a consequent rise in pulmonary pressure. The degree of increase in the pain has been slight, and information has been elicited only on careful questioning. The phenomenon has not been a constant finding, but its presence may be of value in the differentiation from angina pectoris.

5. *Variability of duration of pain.* In the vast majority of patients with coronary disease, the pain falls into one of three catagories as regards duration: (a) pain lasting a few minutes only, induced by exercise and relieved by rest (angina pectoris); (b) pain lasting 30 minutes or longer, occurring in repeated attacks, usually during recumbency, and soon leading to a fatal issue or to a typical clinical picture of myocardial infarction (status anginosus); (c) pain lasting several hours to several days and then disappearing completely (myocardial infarction). All of these duration patterns may occur in the pain of pulmonary hypertension. However, the latter pain presents itself in additional varieties, which are rarely encountered in patients with coronary disease. Thus a patient with mitral stenosis or congenital cardiac disease may have a steady substernal feeling of distention enduring for weeks or months, with or without aggravation upon exercise. An individual with status asthmaticus may have pain as long as the paroxysms endure. The presence of a pain identical in location and quality with that produced by coronary disease, but failing to conform to the usual duration patterns of the pain of the latter disorder is, therefore, an indication to consider pulmonary hypertensive pain as a possible cause.

6. *Clinical evidence of right ventricular hypertrophy.* This is one of the most valuable differential points. In the absence of those disorders, such as thyrotoxicosis or anemia and severe anxiety states, which lead to increase in cardiac output, the presence of diffuse forceful pulsations over the whole left precordial area constitutes strong evidence for right ventricular enlargement. In patients with thin chest walls and without dyspnea, it is our impression that this simple clinical phenomenon is likely to be more reliable than electrocardiographic or roentgenologic evidence. Conspicuous evidence of right ventricular enlargement is rare in patients with pain due to coronary disease. Such patients usually present either no signs of cardiac enlargement, or the forceful, heaving, localized apical impulse of left ventricular hypertrophy. Thus simple inspection and palpation of the chest wall will frequently furnish information of crucial importance in the differential diagnosis of the cause of the pain.

7. *Electrocardiographic changes* may or may not be present in patients with pulmonary hypertensive pain. Thus their absence, while of no value in excluding angina pectoris, con-

stitutes evidence against myocardial infarction as the cause of the pain. When present in patients with pulmonary hypertensive pain, the electrocardiographic changes usually follow the patterns described in patients with acute cor pulmonale following pulmonary embolism.[2, 14, 17, 18] For details concerning the electrocardiographic changes the reader is referred to these publications. It is sufficient here to emphasize that: (1) The electrocardiographic changes are usually those of right axis deviation or right ventricular strain. (2) T-wave alterations suggestive of posterior infarction are not unusual, and occasionally changes suggestive of anterior infarction are seen. (3) Changes characteristic of myocardial infarction may occur because the conditions may coexist.[17] (4) Many of the patients display no characteristic changes. Thus electrocardiograms may be useless or very helpful in differentiating pain associated with pulmonary hypertension from that due to coronary disease. Unless interpreted with extreme care, they may be actually misleading, and may be responsible for an erroneous diagnosis of myocardial infarction. (See electrocardiogram with cases 1 and 6. A diagnosis of coronary occlusion was made in case 1.) This has happened in a number of patients observed personally.

8. *Evidence of tissue destruction* (fever, leukocytosis, rapid sedimentation rate) occurs in patients with pulmonary hypertensive pain only when there is coexistent infarction or infection of the lungs. The presence of such evidence is, therefore, of value in excluding angina pectoris; the absence of such evidence may be of crucial importance in excluding myocardial infarction.

9. *The effect of oxygen.* Striking relief of pain as the result of oxygen inhalation speaks for pulmonary hypertensive pain; slight or no relief may be encountered either with this type of pain, or with that due to coronary disease.

10. *The effect of drugs* may be of crucial importance in diagnosis. Adrenaline may induce or aggravate the pain of coronary disease; it tends to relieve pulmonary hypertensive pain when bronchial asthma is the underlying disease process. Unfortunately, adrenaline is dangerous in patients with coronary disease, and thus its usefulness in differential diagnosis is limited.

Aminophylline may relieve either pain upon intravenous administration. In our experience, relief following rectal or oral administration is more likely to occur when the pain is associated with pulmonary hypertension than with coronary disease.

Nitroglycerin has either no effect or only a minimal palliative effect on pulmonary hypertensive pain. This does not aid in differentiating the syndrome from myocardial infarction but is of great importance in excluding effort angina or status anginosus. We have followed a number of individuals who were diagnosed 15 or 20 years ago as having angina pectoris, but who obtained little or no relief from nitroglycerin. Most of these subjects are now recognized as having pulmonary hypertensive pain, and we believe that our original diagnosis of angina pectoris was incorrect. At the present time we are unwilling to make a positive diagnosis of angina pectoris in the absence of evidence of striking benefit from nitroglycerin.

The points which have been mentioned will usually suffice to allow an accurate differentiation between the pain associated with pulmonary hypertension and that due to coronary disease, in spite of the great similarity of the two conditions. Such a differentiation cannot be made quickly, and especially not by the usual brief clinical examination followed by electrocardiograms. The distinction depends rather upon judicious interpretation of a meticulously conducted examination, and especially upon thoroughness in history taking.

The prognosis in patients with pulmonary hypertensive pain appears to be much better than that in subjects with coronary disease. Sudden unexpected death may occur in subjects with pulmonary embolism, and in those with marked arterial anoxia, but it is less likely to occur than in patients with coronary disease. Frequent, severe, and prolonged attacks of pain have a less ominous significance than in the case of coronary disease. In general, the prognosis is that of the underlying causative disorder. The treatment,

likewise, is essentially that of the underlying disease. In addition, oxygen and rectal aminophylline often are beneficial.

When we turn from the clinical to the physiologic aspects of this syndrome, a number of interesting points arise:

1. *Why is the pain so similar to that produced by disorders of the coronary circulation?* The answer would appear to be that the afferent nerves from the pulmonary artery enter the nervous system by way of the same pathways as those from the heart. The rich networks of nerve fibers in the pulmonary artery pass to the anterior and posterior pulmonary plexuses, and thence by way of the vagi and the upper four dorsal sympathetic routes to the central nervous system. The identical pathways are followed by nerves from the heart. Furthermore, there are many interconnecting fibers between the pulmonary and cardiac plexuses.

2. *What is the exact mechanism of the production of the pain?* Several theories have been proposed, but none has been definitely established. For a review of them the reader is referred to the report of Burgess and Ellis.[1] The presence of the pain in individuals without cyanosis, and its absence in instances of the tetralogy of Fallot, make unlikely the idea that arterial anoxia is responsible. Since it has been shown that anoxia produces constriction of the pulmonary vessels,[19, 20] the dramatic benefit produced in some patients by oxygen can perhaps be ascribed to dilatation of pulmonary vessels, and consequent decline in pulmonary pressure.

The concept of decline in coronary blood flow consequent to decline in cardiac output is not compatible with the demonstration by Cournand and co-workers[19] of high cardiac output in most instances of cor pulmonale. The idea of reflex coronary constriction is not supported by the direct experiments of Katz,[21] by the type of electrocardiographic changes usually encountered, or by the failure of response to nitroglycerin.

The idea that the pain may be the result of pulmonary arteriosclerosis is disproved by its sudden onset following pulmonary embolism.

The concept that this pain represents right ventricular angina, and is the result of mechanical hindrance to systolic coronary flow consequent to increased right intraventricular pressure, is attractive. The chief evidence against it is the failure to respond to nitroglycerin.

It is perhaps more likely that the pain arises in the pulmonary artery itself, and is the direct result of distention of the vessel. The mechanism would, therefore, be somewhat analogous to that of migraine. This hypothesis is supported by the patients in our series. Each of them had clinical evidence of pulmonary hypertension, and the ones who came to necropsy displayed dilatation of the pulmonary artery. In the absence of convincing evidence to the contrary, this hypothesis would seem to offer the simplest and most likely explanation.

3. *What is the reason for the striking relationship of the pain to muscular exercise in certain patients?* If one accepts the idea that the pain is the result of distention of the pulmonary artery as the result of increased pressure, the studies of Hickam and Cargill[22] probably furnish the answer to this question. They found that exercise which produced no rise in pulmonary arterial pressure in healthy subjects led to a well marked rise in persons with emphysema or mitral stenosis.

Summary

1. Chest pain associated with increased pulmonary arterial pressure is infrequently discussed in the recent literature. Perhaps the reason for this is that this pain mimics that of coronary disease so closely that it is usually misdiagnosed as angina pectoris or myocardial infarction.

2. This pain, though identical in character and location with the pain of coronary disease, differs in certain other respects. The differentiation from pain due to coronary disease is considered in some detail.

3. Six case summaries are presented and commented upon.

4. Although the mechanism of the pain is not established beyond question, it is believed that distention of the pulmonary artery consequent to pulmonary hypertension is the most

likely cause. Evidence for this conclusion is presented.

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A Study of the Digitalis-like Action of Thevetoidin in Man

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The effect of thevetoidin in heart failure has been studied. Thevetoidin has a prompt and partly transient digitails-like effect which is shown on the heart rate, the circulatory velocity and on the P-R and Q-T intervals of the electrocardiogram, and also a cumulative effect similar to that of strophanthin. Due to its intense vagal effect and its quick digitails-like action, paroxysmal auricular tachycardia was stopped in two patients out of three in from three to four minutes. Its therapeutic advantages and disadvantages are discussed.

A NEW cardioactive substance, thevetoidin, has been isolated from *Thevetia gaumeri*, in the Department of Physiology and Pharmacology of the National Institute of Cardiology, Mexico. *Thevetia gaumeri*, which grows in various states of the Mexican republic, was identified botanically by Martínez[1] in Mexico and by Woodson[2] in the United States. The chemical extraction of thevetoidin from the seeds of this plant was accomplished by E. Sodi-Pallares and R. Mendez[3, 4] and the pharmacologic study was done by Mendez and collaborators.[5]

Thevetoidin is a white, crystalline, moderately hygroscopic powder. Recent chemical studies still in progress have shown that the thevetoidin used in the present work contains a cardiac glycoside, acetylthevetin, and a small amount of a quaternary ammonium base which has been identified as diacetylisomuscarine. Pharmacologic studies revealed that this substance in a concentration of 1×10^{-4} caused systolic arrest of the frog heart (method of Straub-Fuehner) in 20 minutes. The arrest was shown to be reversible on washing with Ringer's fluid. The minimum lethal dose in the frog obtained by the official method of the U.S.P. XIII is 2.6 mg. and by the method of Hatcher and Brody (technic of Storm van Leeuwen), 2.3 mg.

Experiments carried out by one of us (R. M.) in the insufficient heart of the heart-lung preparation[7, 8] have shown that thevetoidin can reverse experimental cardiac insufficiency, whether spontaneous or induced by pentobarbital. In a dose of 0.8 mg. the effect was transient, failure reappearing within 50 to 60 minutes in the same degree as existed before administration of the drug. In the dog anesthetized with pentobarbital (20 mg. per Kg.) and chloralose (80 mg. per Kg.) a dose of thevetoidin of 0.5 to 0.6 mg. per Kg. produced toxic effects which consisted of bradycardia and prolongation of the P-R interval, followed by auriculoventricular dissociation and multifocal ventricular extrasystoles. These toxic effects on ventricular automatism disappeared rapidly and the P-R interval returned to its normal duration within approximately one to two hours.

With these data as a background we undertook a clinical study of thevetoidin, believing that we were dealing with a substance with a very rapid transient action similar to that of thevetin and of acetylstrophanthidin studied by Gold and collaborators.[9, 10] However, analysis of the cases which we present in this paper demonstrates that the new substance possesses, in addition to the rapid and transient action revealed in the pharmacologic study, a cumulative tendency similar in degree to that of strophanthin.[11]

CASE MATERIAL

The clinical results which constitute the theme of this preliminary work have been obtained in 10 patients with rheumatic heart dis-

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A preliminary report of this investigation was presented at the first International Congress of Cardiology in September, 1950.

ease, seven of whom were in a state of cardiac insufficiency and three of whom had paroxysmal auricular tachycardia. Of those patients in heart failure, two had mitral and tricuspid valvular disease with auricular fibrillation but without active rheumatic disease; two had similar lesions with fibrillation and active rheumatic disease; one patient with lesions of the mitral, aortic, and tricuspid valves had a normal sinus rhythm and an active rheumatic process; one had mitral stenosis and regurgitation and one had lesions of the mitral and aortic valves, both having sinus rhythm and inactive rheumatic disease.

Methods

The patients (except those treated for paroxysmal auricular tachycardia) were maintained at rest for several days before experimentation. In only one patient had any preparation of digitalis been administered for at least 10 days previously. The heart rate and electrocardiographic changes were carefully recorded. In the patients with fibrillation, measurements of the Q-T interval were studied in groups of 10 beats, relating each Q-T interval with the preceding R-R interval. The circulation time was measured by means of potassium cyanide.

Thevetoidin was always administered by vein. Due to the hygroscopic nature of the substance the thevetoidin was stored in evacuated ampoules and dissolved in a volume of 1 or 2 cc. of physiologic saline immediately before injection.

Results

Group 1

(a) *Patients with Mitral and Tricuspid Lesions and Auricular Fibrillation, but without Active Rheumatic Disease* (two cases). The first patient (No. 18610.B2), a girl 18 years of age weighing 48.2 Kg., had been hospitalized several times in the Institute of Cardiology and on each occasion was treated by the classic methods of digitalization. The second (No. 23673.B3), a woman 25 years of age weighing 50 Kg., hospitalized for the first time, was treated first with thevetoidin and several days later with Digilanid. Due to the advanced state of the lesions of these two patients, the improvement which was obtained in the clinical signs with Digilanid and with thevetoidin, although clear, did not constitute a dramatic reversal of the cardiac insufficiency. However, slowing of the heart rate, decrease in liver size, and reduction of jugular engorgement, of edema, and of effort dyspnea with resulting subjective improvement, were as great with thevetoidin as with Digilanid.

Figure 1 shows the changes of heart rate in one of these women after daily injections of thevetoidin. Each injection of 10 mg. (0.2 per Kg.) caused a decrease in the heart rate. The dots on the graph show control rates taken just before each injection. In figure 1 the rate is seen to decline from 130 to 73 after the administration of 27.5 mg. of the drug in three days. Subsequent injections (40 mg. in five days) reduced the heart rate even further to 64 beats per minute. In the second patient a similar decrease of rate after approximately the same dosage of thevetoidin was observed. Return of the heart rate to the level obtained prior to treatment developed gradually over a period of approximately five days.

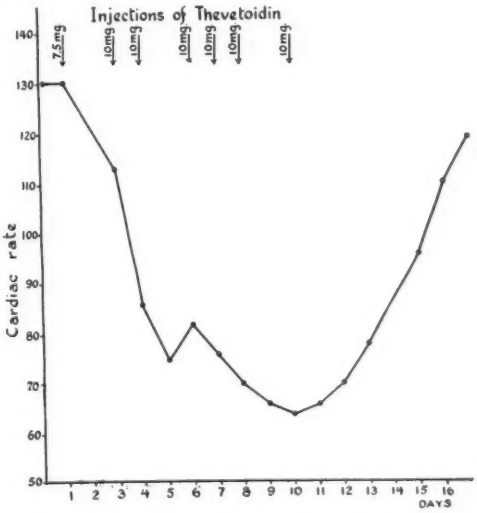

Fig. 1. Cumulative action on the heart rate of repeated injections of thevetoidin. REG. 18610, 18 year, 48.2 Kg. Inactive rheumatic valvular disease, mitral stenosis and regurgitation, tricuspid insufficiency, auricular fibrillation, and cardiac insufficiency grade III.

The fundamental difference between the effects produced in these patients by the classic cardiac glycosides and by thevetoidin was that with the latter substance the maximum re-

sponse was obtained within 10 to 12 minutes after each injection. The effect on the heart rate regressed slowly after this time but the heart rate on the day following the injection was always less than that before injection until, after repeated doses, it was reduced to a controlled level. That is to say, thevetoidin appears to exert a double effect: the first rapid, with a maximum effect at 10 to 12 minutes after injection, and the second slow and cumulative. Figure 1 demonstrates this latter action and figure 2 illustrates the former. The irregularity

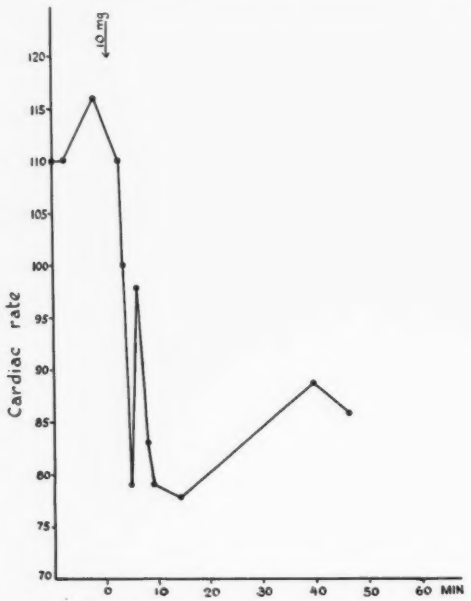

FIG. 2. Rapid effect on heart rate of a single injection of thevetoidin. Same patient as figure 1.

in the heart rate shown in figure 2 was due to a brief period of vomiting which occurred four minutes following the administration of thevetoidin.

An early effect was observed on the Q-T interval of the electrocardiogram, an effect which disappeared almost completely one to two hours after the first dose of thevetoidin. Subsequent injections showed a cumulative effect to which we have already referred in describing changes of heart rate. After the second or third dose, there appeared in these patients depression of the S-T segment similar to that observed with the cardiac glycosides; these effects did not regress until three or four days following termination of the treatment.

(b) *Patients with Auricular Fibrillation, Mitral and Tricuspid Lesions, and Active Rheumatic Fever* (two cases). One (No. 1 REG. 10935.C39) was a youth of 15 years weighing 33.2 Kg.; and one (No. 2 REG. 10988.B13), a 43 year old mother weighing 47.4 Kg.

The same, or even one-half, the amount of the drug administered to the two previous patients frequently caused extrasystoles and at times bigeminal rhythm lasting for 10 to 50 minutes in these two patients with active rheumatic fever. Injection was occasionally followed by mild subjective discomfort such as vague discomfort in the precordial region, sensations of heat, pain in the eyes, or paresthesias in the extremities. These sensations disappeared quickly. In the last days of treatment there was observed a more prolonged bigeminal rhythm, with persistence of extrasystoles until the day following the injection.

The manifestations of toxicity in these two patients with active rheumatic disease are to be contrasted with the results obtained in the two patients without rheumatic activity, in whom no effect whatsoever on ventricular rhythm was observed during the 10 days of treatment with daily doses of 0.2 mg. per Kg.

(c) *Patients without Rheumatic Activity and with Sinus Rhythm* (two cases). The first (REG. 22241.C8), a girl of 15 years weighing 34.2 Kg., with mitral stenosis and regurgitation, received single doses of 5 mg. of thevetoidin daily for four days. Before beginning treatment the heart rate was 102 beats per minute; a presystolic gallop was present. The liver was palpated 3 cm. below the costal border in the midclavicular line and presented grade II pulsations. The circulation time measured with potassium cyanide was 26 seconds (normal, 18 seconds). Roentgenograms of the chest showed grade III cardiac enlargement and pulmonary congestion. On the second day of treatment the heart rate had been reduced to 80 beats per minute with disappearance of the gallop rhythm. The liver regressed to no more than 1 cm. below the costal border and pulsations were estimated at no more than grade I. The circulation time was

reduced to 19 seconds. On the third day the liver had regressed to the costal margin and was no longer felt to pulsate. On the fourth day the circulation time was 16 seconds and x-ray examination demonstrated a definite diminution of the cardiac shadow and of pulmonary congestion (fig. 3).

On the last day when the patient had received a total of 20 mg. of thevetoidin there were occasional extrasystoles and nausea, about three minutes after the injection, which rapidly disappeared. Hours later, vomiting occurred.

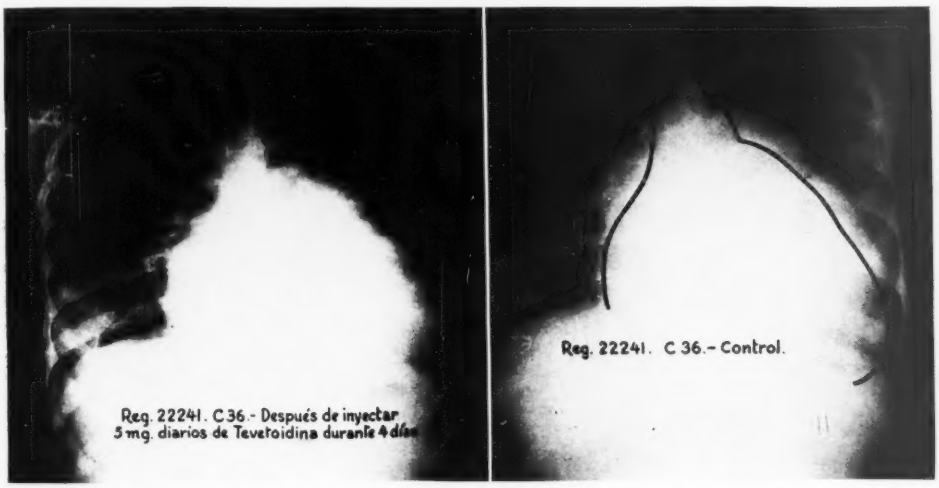

FIG. 3 Reduction of area of cardiac silhouette after daily injections of 5 mg. during four days. The silhouette after injection has been drawn on the figure on the right. REG. 22241, 15 years, 34.2 Kg. Inactive rheumatic valvular disease; mitral stenosis and regurgitation; sinus rhythm. Cardiac insufficiency grade II.

In this patient digitalis-like effects on the Q-T interval similar to those in preceding cases were also observed; to this effect was added prolongation of the P-R interval which increased from 0.18 second as measured on the first day to 0.21 second on the fourth day. The P-R interval returned to the original value of 0.18 second four days after termination of treatment. The early brief action of the drug could be demonstrated also with respect to this measurement, for on the third day it increased from 0.20 second to 0.23 second seven minutes following the injection, only to return to 0.21 second 30 minutes later. The cumulative effects on the P-R interval and the Q-T interval in this case are presented graphically in figure 4.

The second case (REG. 18676.C36), a boy of 15 years, weighing 34.5 Kg., with mitral stenosis and regurgitation and aortic insufficiency, received single daily doses of 5 mg. of thevetoidin during a period of three days. Due to the development of vomiting the dose was reduced to 3.5 mg. daily during the six following days. This dose produced no emetic action. Before treatment the heart rate was 104 beats per minute with a presystolic gallop. The liver margin was palpated 10.5 cm. below the costal border in the midline and 6 cm. in the midclavicular line with grade II pulsations. The venous pressure was 23 cm. of water. The circulation time measured with potassium cyanide was 26 seconds. Twenty-eight minutes following the first injection the circulation time was reduced to 20 seconds.

On the second day the liver margin was 9.5 cm. below the costal margin in the midline and 5 cm. in the midclavicular line; pulsations were reduced to grade I. Except for delayed vomiting no other changes were reported. On the third day the heart rate was 96 per minute and

vomiting occurred one minute following the injection preceded by an ill defined taste and a sensation of numbness in the lower lip. Vomiting occurred again later. On the fourth day the dose was reduced to 3.5 mg. Nausea and a mild pain in the eyeballs appeared after the injection but rapidly receded. The circulation time was reduced to 19 seconds. On the fifth day the liver edge was palpated at 8.5 cm. below the costal margin in the midline and only 2.5 cm. in the midclavicular line; pulsations were no longer

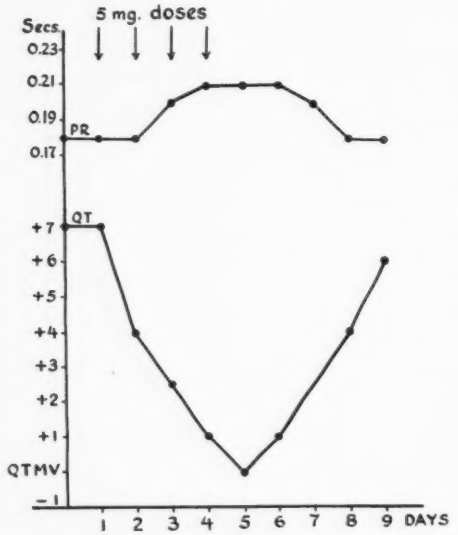

FIG. 4. Cumulative effect of repeated injections of thevetoidin on the P-R and Q-T intervals. REG. 18676, 15 years, 34.2 Kg. Inactive rheumatic valvulitis; mitral stenosis and regurgitation; cardiac insufficiency grade II.

observed. The heart rate was 92 per minute but the gallop rhythm persisted. From the sixth to the ninth day no further variations were observed. On this last day two doses of 3.5 mg. each were administered. A second bout of repeated vomiting lasting several hours followed.

On the tenth day, when treatment was terminated, the heart rate was 90 per minute. Gallop rhythm persisted and the liver was palpated 7.5 cm. below the costal border in the midline and 2 cm. in the midclavicular line. Pulsations were not detected. Circulation time was 20 seconds. Venous pressure was 18 cm. of water. No significant changes were observed in the cardiac size.

The most marked changes in this case were the reduction of liver size and pulsation and of the circulation time and the venous pressure. It is to be emphasized that the diminution of six seconds in the circulation time obtained following the first dose was not improved with subsequent doses. The effects on the P-R and Q-T intervals were similar to those found in the other patients.

Group 2

Paroxysmal Auricular Tachycardia (three cases). The rapid action of thevetoidin with its strong vagal component observed experimentally and in some patients suggested to us the possibility of its use in paroxysms of auricular tachycardia. The first patient, C8, a 15 year old girl weighing 30 Kg., with inactive rheumatic fever and grade I cardiac insufficiency, received an injection of 6 mg. which restored sinus rhythm in four minutes. Paroxysmal tachycardia did not recur during our observation. In the second case, B2, a 16 year old girl weighing 40 Kg., with active rheumatic disease, a dose of 8 mg. caused no effect whatsoever. Six hours later she received 10.5 mg. Two and one-half minutes following this dose there appeared 2:1 and 3:1 A-V block which lasted three minutes; later 1:1 rhythm was reestablished with a prolonged P-R interval, but the paroxysm of tachycardia was not terminated. The third case, C. E., a youth of 20 years weighing 60 Kg. with active rheumatic disease, received 12 mg. Tachycardia ceased within three minutes.

Dosage and Secondary Effects

A daily dose of 0.2 mg. per Kg. of body weight produced complete digitalis-like effects in three or four days. A single injection of 10 mg. in patients weighing approximately 50 Kg. produced nausea and vomiting in almost every case. The time of appearance of this side effect varied between 2 and 15 minutes and the episode was in general of no more than a few minutes duration. Division of the dose into two injections per day each of 0.1 mg. per Kg. with an interval of several hours

between the two injections, almost always prevented the appearance of vomiting. In only one case was a moderate and brief period of nausea observed under this method of administering the drug. In general, children tolerated the strong dose of 0.2 mg. per Kg. better than adults and only on rare occasions was vomiting observed. Other mild transient secondary side effects, such as paresthesias, ocular pain, and a sensation of heat, were observed only occasionally.

We have made no systematic attempt to obtain a rapid digitalis-like effect in less than three days. We believe, however, that with doses appropriately divided full effects of the drug may be obtained in 24 hours or less. In one adult patient with auricular fibrillation, who received 17.5 mg. divided in two injections given six hours apart, a reduction of heart rate from 130 to 80 was achieved.

Demonstration of the Transient Nature of the Toxic Action

One male patient, weighing 36 Kg., with paroxysmal auricular tachycardia probably due to digitalis intoxication, received by error 9 mg. of thevetoidin. One minute later there appeared a salvo of ventricular extrasystoles from four foci. Four minutes after the injection the extrasystoles were less frequent, originating from only two foci, and there was 3:1 and 2:1 A-V block. Five minutes after the injection extrasystoles had disappeared but a 2:1 A-V block persisted. Eight minutes after injection an episode of auricular fibrillation of only one minute duration appeared. By 10 minutes much of the evidence of intoxication had disappeared. The auricular tachycardia continued.

Discussion

The results demonstrate that thevetoidin possesses a typical digitalis-like action and that within this general action there may be distinguished two different effects. The first is characterized by an early, rapid and partially reversible action on the heart rate, A-V conduction, the Q-T interval and by the production of brief toxic effects (transient extrasystoles, nausea and vomiting). The second effect is characterized by a cumulative action similar to that of strophanthin.

Pharmacologic study of thevetoidin demonstrated the first of these two actions. With appropriate doses the action on the insufficient heart in the heart-lung preparation was very rapid: the effect reached a maximum in approximately 10 minutes only to diminish progressively until within an hour insufficiency of the degree present before injection was reestablished. This rapid action and its early disappearance were confirmed by experiments on anesthetized dogs in which digitalis-like toxic effects produced by one injection of thevetoidin rapidly disappeared. The later and more persistent effect has been demonstrated by the clinical studies described in the present paper. These studies showed that in addition to the rapid action a clear cumulative effect develops which suggests one of the two following possibilities: first, that thevetoidin possesses two different effects, one brief and one persistent; second, that thevetoidin contains two substances each responsible for one of the two effects. Since thevetoidin has recently been shown to contain small amounts of a muscarin derivative in addition to a cardiac glycoside, the early effect might be due to the combination of the action of the quaternary ammonium base with the fast-acting glycoside. The vagal effect caused by the quaternary ammonium base should at least be partly responsible for the effect in patients with paroxysmal auricular tachycardia.

The small number of cases studied does not permit us to fix precisely the limits of dosage. However, it appears almost certain that one may expect adequate digitalis-like effects with the administration of 0.2 mg. per Kg. divided in one, or better two, daily injections during three or four consecutive days.

While considering dosage it is important to discuss the side effects of the drug. The mild subjective symptoms described are brief and of only minor significance. On the other hand, the frequency of vomiting marks thevetoidin as a digitalis-like substance which provokes this side effect with great facility. Clinically, this constitutes a great inconvenience. Fortunately, we have found that dividing the dose or reducing it

slightly lessens or even eliminates vomiting. The results obtained with the prophylactic administration of Dramamine to two patients suggest the use of this drug to avoid vomiting following the administration of thevetoidin.

With respect to its surprising speed of action thevetoidin possesses a great advantage over strophanthin, being comparable only with thevetin and acetylstrophanthidin, as studied by Gold and collaborators.[9, 10] Thevetoidin, however, possesses a cumulative action. It is not apparent from the studies of Gold whether thevetin and acetylstrophanthidin are similar in this respect since their experiments were limited to observation of acute effects of a single injection on the heart rate without electrocardiographic records or observation of changes in the degree of cardiac insufficiency.

The speed of action of thevetoidin is unsurpassed by any other known cardiac drug. The drug slows the heart rate, increases the circulatory velocity and improves the work of the heart. It has not been used in the treatment of acute cardiac failure for fear of its emetic effect. A glycosidic substance purer than thevetoidin will shortly be used for the treatment of this condition.

By virtue of its cumulative action, which prolongs its effects for several days, thevetoidin has proved to be very efficacious in the treatment of chronic cardiac insufficiency. In the course of three or four days we have been able to achieve digitalis-like effects with variable results according to the type of the patient treated; in some elimination of cardiac insufficiency was complete, in others only improvement was obtained, but in the latter cases the complete correction of insufficiency was impeded by the presence of advanced tricuspid lesions or rheumatic activity. Furthermore, in these same patients digitalis itself failed to restore a complete state of compensation. The major advantage of thevetoidin in cases of chronic insufficiency appears to be based on the low incidence with which persistent arrhythmias are produced. Patients who were unable to tolerate digitalis because of the rapid development of bigeminal rhythm have responded well to thevetoidin with only occasional transient extrasystoles. One patient already intoxicated with digitalis who received by accident a dose of thevetoidin developed an arrhythmia, but this disappeared in the course of only a few minutes while arrhythmia due to digitalis may be expected to last for a long time.

It seems apparent that thevetoidin may be a product more controllable than digitalis in the early cardiac insufficiency following myocardial infarction. In this situation fear of provoking grave arrhythmias at times prevents the use of digitalis. Thevetoidin could be equally useful but less dangerous. Later studies will permit us to confirm or deny this point.

Summary

Thevetoidin, a cardioactive substance obtained from a Mexican species of *Thevetia* has been subjected to clinical study. This study has been carried out in 10 rheumatic patients, seven of whom were in a state of cardiac insufficiency with or without auricular fibrillation, and three of whom had paroxysmal auricular tachycardia.

The results obtained with thevetoidin in cardiac insufficiency were analogous to those obtained with digitalis in the same patients.

Of the three patients treated during paroxysmal tachycardia, normal sinus rhythm was restored in two within three to four minutes following injection of the drug.

Thevetoidin has an early action on heart rate, on circulatory velocity, and on the P-R and Q-T intervals of the electrocardiogram, effects which reach their maximum within 10 to 12 minutes. In addition to this early action it possesses a cumulative effect similar to that of strophanthin which permits the satisfactory treatment of chronic cardiac insufficiency. The transient nature of the effects of thevetoidin is apparent with respect to the early toxic manifestations, such as vomiting and ventricular extrasystoles.

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The Treatment of Hypertension with Hexamethonium

By EDWARD D. FREIS, M.D., FRANK A. FINNERTY, JR., M.D., HAROLD W. SCHNAPER, M.D., AND CAPTAIN ROBERT L. JOHNSON, M.C., U. S. A. F.

Hexamethonium by subcutaneous injection in doses of 10 to 75 mg. of the ion every 8 or 12 hours produced significant reductions of arterial pressure and symptomatic improvement in a high percentage of patients with benign or malignant hypertension. Methods for preventing tolerance and undesirable side effects are presented, and the advantages as well as the limitations of hexamethonium therapy are discussed.

IN 1948 Paton and Zaimis[1] introduced a series of polymethylene bistrimethylammonium compounds of which the decamethonium (C10) member exhibited curariform properties while the penta- and hexamethonium (C5 and C6) compounds produced a blockade of all autonomic ganglions.

Arnold, Goetz and Rosenheim[2] and Burt and Graham[3] demonstrated the marked vasodilator and hypotensive properties of pentamethonium in man. Kay and Smith[4] noted a marked reduction of gastric acidity after hexamethonium in patients with peptic ulcer, this effect apparently being due to inhibition of the parasympathetic nervous system. Favorable reports[5–8] have appeared concerning the use of C5 and/or C6 in the treatment of essential hypertension.

Previous studies in this laboratory indicated that hexamethonium, C6, produced greater vasodilatation in the toes than either tetraethylammonium or Priscoline.[9] Quantitative measurements of the increase in foot blood flow after 50 to 100 mg. of C6 ion in normal subjects suggested that this compound produced nearly complete blockade of the sympathetic outflow to the foot[10] and was, therefore, considerably more potent than previously known vasodilator agents.[11] The present communication outlines our experience to date with C6 in the treatment of hypertension. The dosages of hexamethonium given in this paper refer to the amount of C6 ion rather than of the salt hexamethonium dibromide.

TIME-DOSE RELATIONSHIPS

Following the intravenous administration of 5 to 50 mg. of C6 ion (9.6 to 96 mg. of hexamethonium dibromide) the cardiovascular effects of the drug appeared within two to three minutes and quickly reached a maximum within 10 minutes or less. These effects consisted of a reduction of blood pressure and increase of heart rate, both of variable degree, as well as a consistent marked postural hypotension. Following the larger doses there also was a marked increase of foot blood flow and digital skin temperature. The peak of these effects usually lasted 15 minutes after which there was a gradual waning over a period of 5 to 10 hours. The heart rate usually increased only slightly and at times actually decreased.

By the intramuscular and subcutaneous routes responses occurred at 15 to 30 minutes following injection and persisted for a period similar to that observed after intravenous administration.

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Hexamethonium dibromide (Bistrium) was supplied by H. Sidney Newcomer, M.D., E. R. Squibb and Sons, New York, N. Y.

Effect of Oral Administration of Hexamethonium

A previously untreated 49 year old man with essential hypertension was given 25 mg. of C6 intravenously with a reduction of blood pressure from 220/120 to 160/95 and a further fall to 110/70 on sitting up in bed. The next day he was given 0.5 Gm. of C6 ion orally in the form of the dibromide salt. One hour later the blood pressure had fallen from 225/125 to 190/115 with a further reduction to 150/110 on standing upright. Two hours later the blood pressure rose to the control values and the postural hypotension had disappeared.

The next morning the patient was given 0.8 Gm. of C6 ion after breakfast. There was no significant reduction of arterial pressure until three hours after the dose had been taken when the blood pressure was unchanged with the patient in the supine position but in the erect position it fell from 210/130 to 160/115. At five hours the patient complained of feeling cold (a reaction we have noted when the increase in peripheral blood flow is intense). The blood pressure was 170/115 supine and 120/90 erect. At eight hours he felt weak and listless and was unable to stand without faintness. The blood pressure was 160/110 supine and 110/80 on sitting up in bed. At 10 hours the blood pressure supine was 130/80 and the patient developed nausea and vomiting. Following this the blood pressure rose gradually and at 24 hours it was 180/100 with no postural hypotension. Thus, a dose of 0.5 Gm. had produced only a transient and minimal response whereas the next day a dose of 0.8 Gm. had resulted in a delayed and profound degree of autonomic blockade. Similar unpredictable responses were seen in two other cases who were given single daily doses of C6 orally.

Three hospitalized patients who had exhibited satisfactory hypotensive responses to parenteral C6 in doses varying from 10 to 25 mg. twice daily were given the drug orally in amounts varying from 0.25 to 1.0 Gm. of C6 ion every 12 hours for periods ranging from five days to two weeks. In all of these patients the hypotensive response usually was considerably less marked and more fleeting than after parenteral dosages. It was apparent that these large oral doses were insufficient, suggesting that almost the entire amount had been destroyed in the gastrointestinal tract. However, on occasion marked reductions of blood pressure occurred accompanied by severe postural hypotension suggesting that the rate of destruction and absorption was sporadic and, hence, unpredictable.

Toxic Reactions

The "toxic reactions" to the drug appeared to be due entirely to the blockade of autonomic ganglions. In hypertensive, elderly and debilitated patients sudden and profound reductions of blood pressure to collapse levels have occurred even when the patients were in the supine position. Parenteral doses as small as 10 mg. may precipitate these marked hypotensive reactions. Almost always they occurred after the initial injection and, when dosages were repeated several times per day, the blood pressure reduction was more moderate. However, if the drug was discontinued for four or five days or longer an injection of C6 might be followed again by a marked fall of arterial pressure. In general, the greater the interval between injections of C6 the more marked and long lasting the reduction of blood pressure following each injection.

All patients exhibited marked postural hypotension which persisted for four to six hours or even longer but was severe only during the first three hours after the drug. During continued administration of C6, particularly if the drug was given at frequent intervals (four to six hours apart) the postural effect diminished in intensity. With less frequent administration (8 to 12 hour intervals) considerable but not disabling postural hypotension was retained for as long as our observations have been carried out (five months).

Approximately two-thirds of the hypertensive patients complained of constipation. In addition, in four cases a condition resembling paralytic ileus occurred during the first week of treatment which was manifested by distention, obstipation, absence of peristaltic sounds on auscultation of the abdomen and nausea. In

one instance fluid levels were seen in the small bowel by roentgenography.

The constipation and ileus apparently were due to the marked inhibition of gastrointestinal tract motility produced by the blockade of the autonomic nervous system, particularly the parasympathetic system.[12] For this reason we have used more recently, to restore bowel motility, parasympathomimetic agents, the most satisfactory of which has been the urethane of β-methylcholine (Urecholine) in doses of 5 to 20 mg. (average dose 10 mg.) under the tongue two to three times per day. If constipation continued despite tolerated doses of this drug, laxatives such as mineral oil and magnesium hydroxide were used in addition. However, since Urecholine has been used no further cases of ileus have been encountered. The drug also prevented the dryness of the mouth complained of in a few patients.

Four hypertensive patients complained of urinary retention. This difficulty also occurred early in treatment and disappeared following temporary reduction of dosage. It probably also is due to parasympathetic blockade and has not been observed since the introduction of parasympathomimetic agents into the treatment regimen.

Dosage Adjustment

In all cases over the age of 40 and in all debilitated or hypertensive patients the initial dosage level was determined as follows: while the blood pressure was being recorded once per minute in the opposite arm, the patient being propped up slightly in bed, C6 was injected at a rate of 1 mg. of the ion per minute until a total of 10 mg. had been administered. If there was no significant fall of blood pressure the rate of administration was increased to 2 mg. per minute until an additional 10 mg. had been given and then at a rate of 5 mg. per minute to a total of 50 mg. As soon as a slight reduction of blood pressure occurred the injection was temporarily halted for two to three minutes in order to determine whether a further fall of pressure would occur.

If, at any time during this trial period, there was a profound fall of blood pressure, the pillow was removed from beneath the patient's head and he was placed in a head-down position by tilting the foot of the bed on shock blocks. The lower extremities were elevated and passively exercised. If this failed to restore the blood pressure the intravenous administration of 2 to 5 mg. of phenylephrine hydrochloride (Neosynephrine) intravenously quickly elevated the blood pressure to normal levels. These severe hypotensive reactions occurred prior to the institution of the method for determining the initial dosage outlined above. They were sufficiently frequent to make it obligatory that a physician administer the first dose of the drug and that an assistant follow the blood pressure response in order to arrive at a dose level that was safe for the particular case. When these precautions were taken severe collapse reactions have been avoided.

After the effective dose had been determined, this amount was administered every 8 to 12 hours by subcutaneous injection since shorter intervals between doses seemed impractical for chronic therapy of hypertension. The initial dosage level seldom was effective beyond several days so that it was necessary to increase each dose by an amount of 5 to 15 mg. and further increases were made as necessary to a total of 50 mg. of the ion. Even larger doses have been used in occasional resistant cases. In such instances larger doses not only produced a greater but also a more prolonged reduction of blood pressure.

In some patients, however, the hypotensive effect did not persist beyond six hours. In such cases various drugs were used in an attempt to maintain the hypotensive response, the most effective of which was 1-hydrazinophthalazine (C-5968)* given orally midway between the doses of C6. The initial dose of C-5968 was 25 mg. and this was increased at intervals of 24 hours by increments of 25 mg. until the patient manifested a significant hypotensive response or until side effects such as severe palpitation occurred. The effective dose of C-5968 usually varied between 50 and 150 mg. Like C6 this drug usually could not be given more often than every 12 hours without the appearance of side effects, particularly head-

* Generously supplied by Frederick Yonkmann, M.D., Ciba Pharmaceuticals, Summit, N. J.

aches, as well as the development of tolerance. A complete description of the results obtained with C-5968 will be reported elsewhere.[13]

Results in Hypertensive Diseases

Thirty-two patients have been treated for periods varying between one and five months. All except one were hospitalized prior to and at the onset of treatment. Fourteen of these cases exhibited malignant hypertension, two had chronic glomerulonephritis, while the remaining patients had varying degrees of sustained diastolic blood pressure of 110 mm. Hg or higher. The two patients with chronic glomerulonephritis and uremia exhibited reductions of blood pressure and temporary symptomatic improvement, but died within one and two months respectively of their uremia.

Malignant Hypertension

Of the 14 cases of malignant hypertension, six showed a good result following the use of C6, four exhibited remissions using C6 and C-5968 in combination[13] and four, three of whom had advanced renal failure, had a poor result. All except one of these patients also were administered diets containing 200 to 500 mg. of sodium per day. However, this probably was not necessary in all cases and in each patient it was possible to demonstrate the hypotensive effect of hexamethonium in the results obtained.

Case 1. R. D., a 52 year old housewife, was first seen with malignant hypertension one year previously. Treatment with a diet containing 200 mg. of sodium per day and Anatensol* resulted in a remission lasting approximately eight months. The malignant phase then gradually returned despite treatment and in November 1950 the patient once again exhibited marked neuroretinitis. The blood pressure, recorded three times daily either by the patient's husband or a visiting physician, was relatively fixed at 250/140. There was weight loss from 110 to 94 pounds, anorexia, nausea and vomiting, constant headache, and nocturia five to six times. The blood nonprotein nitrogen was 39 mg. per 100 cc.

Hexamethonium was begun on Nov. 2, 1950, 25 mg. every six hours, with an immediate fall of blood pressure to approximate levels of 190/120 (fig. 1). The dose was reduced to 25 mg. every 12 hours, but because of elevations of pressure in the morning, the frequency of doses was increased to every eight hours. During the first two weeks there was severe obstipation, nausea, vomiting and faintness. However, all symptoms began to regress and within two months the fundi had cleared completely except for residual scars. After 14 weeks the number of injections was reduced to two a day, but the dose was increased to 38 mg. with maintenance of reduced levels of blood pressure (fig. 1).

After five months of treatment with C6, the patient had a good appetite and weighed 106 pounds. The nocturia, headaches and nausea disappeared. Following each injection of C6 she found it necessary to remain supine for one to two hours because

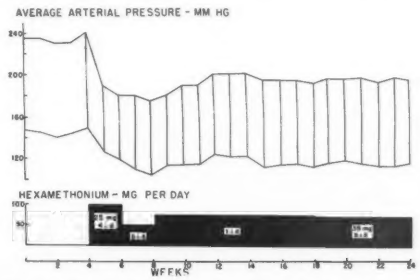

FIG. 1. Chart of the average arterial blood pressure and dosage of hexamethonium in case 1, R. D., a white woman, aged 52 years, with malignant hypertension. Each point in the chart of arterial pressure represents the average of at least 28 separate determinations, all being recorded with the patient in the supine position. See text for further details.

of the postural hypotension. Throughout treatment the blood pressure levels fluctuated, markedly dropping one-half to one hour after each injection and then slowly rising until the next dose of C6. Even after five months, during a single day it was not unusual for the recorded pressures to vary between 160/95 to 210/130 mm. Hg. Because of persistent constipation, laxatives daily and enemas several times per week were required until Urecholine plus mild laxation were introduced.

Case 2. T. M. a 52 year old man, was admitted with a blood pressure of 260/170. There was extensive neuroretinitis with many hemorrhages and exudates in the fundi. The blood nonprotein nitrogen was 48 mg. per 100 cc. The patient was placed on a 200 mg. low sodium diet and was given 10 mg. of C6 intravenously on the day of admission. Within five minutes after the drug had been given the blood pressure fell from 260/170 to 100/80 supine. Despite this sudden and profound hypotensive response the patient noted only a moderate sensation of faintness. When this dose was repeated every four hours

* Purified extract of veratrum viride. E. R. Squibb & Sons, New York, N. Y.

the blood pressure rose and, despite elevation of dosage to 25 and even 50 mg. repeated every four hours, the general level of blood pressure returned to nearly control values (fig. 2). The interval between doses was then increased to 12 hours and this was followed by a fall in pressure to normotensive levels. After three weeks the blood pressure fell to 80/60 and the patient complained of marked faintness. Hexamethonium was discontinued and the patient was given 1000 cc. of saline intravenously. He improved immediately, the blood pressure rising to 130/100. The sodium content of the diet was increased to 500 mg. per day. C6 was omitted for the next 10 days and the blood pressure gradually rose

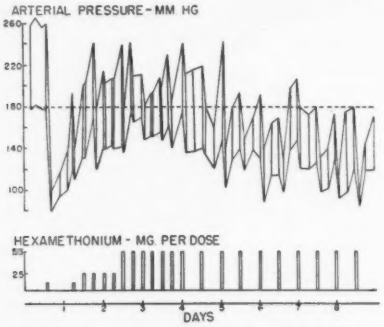

FIG. 2. Chart of the arterial pressure and dosage of hexamethonium in case 2, T. M., a white man, aged 52 years, with malignant hypertension. All blood pressures were recorded with the patient in the supine position. Note (1) the marked hypertensive response to a small initial dose of C6, (2) the apparent development of tolerance when doses were administered at frequent intervals, (3) the return of a significant hypotensive effect when the doses of C6 were separated by an interval of 12 hours, and (4) the typical marked fluctuations of blood pressure during each day while under treatment. See text for further details.

to a level of 170/120. The drug was again given in doses of 10 mg. every 12 hours, the blood pressure falling to average values of 140/100, where it remained for the succeeding month. The hemorrhages and exudates disappeared from the optic fundi although slight papilledema still remained. At the end of the next month the papilledema had cleared completely, the nonprotein nitrogen was 36 mg. per 100 cc. and the patient was ambulatory and felt considerably improved.

Hypertension Other Than Malignant

There were 16 patients in this group, of whom 10 exhibited a continued, average reduction of blood pressure greater than 25 mm. Hg systolic and 10 mm. Hg diastolic. Of this number seven exhibited sustained reductions of average pressure varying between 40 and 60 mm. Hg systolic, and six of these maintained reductions of diastolic pressure varying between 20 and 40 mm. Hg. Two of the patients who had a good result exhibited grade III changes in the fundi; all of the others being grade II. Of the patients who exhibited a poor response, three exhibited grade III changes, two grade II, and one manifested grade I fundi. Thus, there was no relationship between the severity of the hypertension and the therapeutic result obtained.

Some of the cases manifesting poor results were treated in the earlier stages of the investigation. They were failures either because resistance to the hypotensive effects developed quickly, or the duration of the hypotension was brief or was insignificant in the supine position. Several of the more recently treated patients, who appeared to be resistant to C6 alone, have exhibited a satisfactory hypotensive response when the dosage was raised and/or when C-5968 was added to the treatment regimen.[13]

DISCUSSION

The results obtained to date with the use of hexamethonium in the treatment of hypertension are in essential agreement with the prior observations of Smirk[14] and other investigators.[5–8] The combined experience of these various studies leaves little doubt that hexamethonium provides a method for reducing blood pressure in a large percentage of hypertensive patients, and that this reduction frequently is accompanied by relief of some of the signs and symptoms associated with the disease. The ability to induce a significant therapeutic response in 10 of the 14 cases of malignant hypertension either with C6 alone or in combination with a low sodium diet and/or C-5968 represents in our experience a higher percentage of remissions than would be anticipated with other known methods of treatment.

The advantages of C6 are its ability to produce and to maintain for long periods a significant hypotensive response in a high percentage of patients, its rapidity of action and simplicity of administration. The disadvantages are (1)

the danger of severe hypotensive reactions due to injudicious dosage administration in the early phases of treatment, (2) the frequent development of constipation and occasionally paralytic ileus, and (3) the inability to obtain a stable level of hypotension throughout the 24 hour period in many patients. Finally, unless the technic of administering oral therapy can be improved, the necessity for continued hypodermic injections imposes a hardship on the patient. Recent evidence suggests that large amounts of hexamethonium dichloride (0.5 to 2.0 Gm. of the ion) given as a single daily oral dose administered at bedtime may be more effective than divided oral dosage.[15]

The most dangerous of the "toxic" reactions is the extreme hypotension that may follow the initial dose of the drug. A fatality has been reported after C6[16] and serious hypotension has occurred also following the less potent and shorter acting ganglionic blocking agent, tetraethylammonium.[17] In both of these reported cases, epinephrine was used to combat the hypotension. Epinephrine has a vasodilator component and, after the pressor response has subsided, the blood pressure does not fall directly to normal, but rather there is a period of hypotension.[18] Epinephrine also induces marked vasodilation in skeletal muscle[19] and, in contrast to norepinephrine and related drugs, produces a decrease rather than an increase in total peripheral resistance.[20] In addition, the ganglionic blocking agent tetraethylammonium increases the sensitivity of the myocardium to epinephrine-induced arrhythmias in dogs under cyclopropane anesthesia.[21] As a result of their study, Stutzman and his co-workers[21] concluded that "epinephrine is contraindicated as a pressor agent after tetraethylammonium chloride." They recommend that phenylephrine (Neosynephrine) be used for this purpose.

The most successful and the safest procedure for treating the collapse reactions following the administration of C6 was to elevate the foot of the bed in order to maintain the cerebral circulation. In addition, further elevation and passive exercise of the lower extremities facilitated diversion of blood into the central circulation.

These severe hypotensive responses almost always occur only after the *initial* injection. Hence, if care is used at this time such reactions should be avoidable. Since we have utilized the method of administration outlined in the "dosage adjustment" section of this paper, severe collapse reactions have not been encountered. The importance of determining the effective initial dose in each case is emphasized by the observation that one patient exhibited a significant hypotensive response after only 3 mg. of C6 ion had been administered intravenously. If 5 or 10 mg. had been injected the patient almost certainly would have had a severe hypotensive reaction. On the other hand some cases have exhibited little hypotensive response in the supine position after an initial dose of 50 mg.

The concomitant administration of a parasympathomimetic agent to alleviate the constipation, ileus, dry mouth and difficulty in urination produced by C6 represents one application of the general principle of circumventing undesirable side effects by utilizing antagonistic pharmacologic agents which, however, do not interfere with the desired therapeutic action. Since parasympathomimetic agents have vasodilator properties they may be expected to enhance the hypotensive effect of C6.

The therapeutic regimen of alternating doses of C6 and C-5968 also seems representative of another principle of hypotensive drug therapy. In our experience all vasodepressor agents produce varying degrees of tolerance. By utilizing alternately agents with different loci of action the development of tolerance to any single agent may be considerably delayed.

Smirk has taught his patients to self-administer hexamethonium by injection in the home.[14] This procedure has been applied successfully in the present study, and, in addition, in many instances a member of the family or the patient has been taught to record the blood pressure. By such frequent measurements of arterial pressure under varying conditions a far more precise indication of the effect of treatment has been obtained.

It should be emphasized that the results of treatment with C6 reported herein are of a

preliminary nature since none of the patients have been treated continuously for longer than five months. In addition, the most effective method of administering the drug or of combining it with other hypotensive procedures cannot be considered to be finally settled. Finally, because the method of administration outlined herein requires repeated hypodermic injections and frequent observation of the patient, at least in the initial phases of treatment, it would seem to be indicated only in the more severe and resistant cases of hypertension.

Summary and Conclusions

Hexamethonium has been administered continuously for periods of one to five months by subcutaneous injection to a series of 32 hypertensive patients with the following results:

1. In 14 cases of malignant hypertension, six have undergone a remission of the malignant phase while four others have exhibited remissions with the addition of 1-hydrazinophthalazine (C-5968) administered orally midway between the doses of C6. Four patients, three of whom had advanced renal failure, did not respond to C6 alone or in combination with other drugs. Two additional patients who had advanced chronic glomerulonephritis exhibited hypotension and symptomatic improvement but died of progressive uremia.

2. In 16 patients with less severe degrees of sustained hypertension, six have shown sustained reductions of arterial pressure after hexamethonium alone, four have responded to a combination of C6 and C-5968 while six others failed to maintain a sustained hypotensive response. Most of the latter cases were treated in the early stages of this investigation when the doses were too frequent and too small.

3. The effective hypotensive dose of C6 ion by subcutaneous injection varied between 10 and 100 mg. Small doses usually lowered the blood pressure after the initial injection but gradually increasing doses were required over a period of days or weeks to attain a stable effective dosage level. C6 was administered at intervals of 8 or 12 hours.

4. Undesirable reactions consisted of (1) occasional severe reductions of blood pressure occurring almost entirely only after the initial injection of C6, (2) postural hypotension diminishing in severity with prolonged treatment, (3) gastrointestinal atony producing constipation occasionally with paralytic ileus and, rarely, (4) difficulty in urination. Methods for circumventing most of these reactions are described.

5. Hexamethonium administered orally in doses up to 1.0 Gm. of the ion to a few patients appeared to be less effective and more unpredictable than parenteral administration.

6. The most effective and best tolerated treatment for the largest number of hypertensive patients was the following: (1) parenteral administration of C6 at intervals of 12 hours in doses of 10 to 75 mg. of the ion depending upon the patient's response, (2) oral ingestion of 50 to 150 mg. of C-5968 midway between the doses of C6 and (3) a diet containing 200 to 500 mg. of sodium per day.

Addendum

After 10 months of continuous treatment all the cases in this series who had responded favorably are maintaining a significant hypotensive effect and they remain clinically improved, except for one patient with malignant hypertension who died suddenly due to a coronary occlusion. In some cases it has been necessary to elevate dosages to as high as 150 mg. of C6 ion in order to overcome tolerance but this has been accomplished without adverse side effects.

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The Effect of 1-Hydrazinophthalazine in Hypertension

By HENRY A. SCHROEDER, M.D.

The compound 1-hydrazinophthalazine appears to be be an antihypertensive drug of only moderate potency. Based on experience with 50 cases of arterial hypertension, it was found most effective in patients with unsuccessful sympathectomy, malignant hypertension, and neurogenic hypertension. It was relatively ineffective in renal hypertension and in a group of miscellaneous conditions. Chronic administration by mouth in outpatients was feasible.

A NEW compound, 1-hydrazinophthalazine (C-5968), has been shown by Reubi[1] to cause hemodynamic effects which suggest that it may act as an antihypertensive agent. After single doses effective renal plasma flow was increased, while blood pressure was moderately lowered in hypertensive patients.[1] Freis and Finnerty[2] found that the cold pressor test was modified by the drug, as well as the vasopressor "overshoot" following the Valsalva maneuver. Pulse volume in digits also increased. Grimson and his co-workers[3] failed to demonstrate sustained effects on repeated administration.

1-Hydrazinophthalazine is the basic structure (fig. 1) for several substituted compounds which have the peculiar pharmacologic properties of increasing renal and femoral blood flow in the dog and rabbit while lowering blood pressure,[4] a characteristic not enjoyed by most other circulatory depressants. The drug is sympatholytic in some animals in that it antagonizes the pressor action of epinephrine[3]; that of hypertensin is also blocked.[5, 8] In man, norepinephrine may be partly opposed. There is suggestive evidence that the depressor effect occurs through action on the hind or midbrain.[4, 6] Methyl and benzene substituted compounds appear to differ but little.[4]

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In October, 1949, an investigation of the effects of chronic administration of C-5968 to renal hypertensive dogs was initiated. The drug was given intravenously in doses of 10 mg. every day or every other day. This regimen resulted in partial or complete control of hypertension without causing nitrogen retention, loss of weight, or other demonstrable toxic reactions.[5]

The characteristics of a true antihypertensive drug include the ability to lower blood pressure (a) without affecting the myocardium adversely, (b) without decreasing renal blood flow, and (c) without altering blood volume or viscosity. Because C-5968 appeared to have the pharmacologic properties of (a) and (b), was relatively nontoxic in dogs and rabbits, and could be administered by mouth, an investigation of its chronic therapeutic properties in hypertension has been conducted on 50 selected patients. This study was begun in September, 1949, and has been reported in abstract form elsewhere.[9–11] The present report deals with the effects on blood pressure and other functions clinically measurable.

METHODS

Fifty patients were selected from the wards of Barnes and St. Louis City Hospitals and from the Hypertension Clinic of Washington University. An attempt was made to obtain as many different types of hypertension as possible, both of the essential and malignant varieties, and those secondary to renal diseases. In hospital, blood pressures were recorded in the supine position at four-hourly intervals by members of the nursing staff; those of outpatients were measured once daily by the same physician at approximately the same hour, after

5 to 10 minutes rest in the supine position and then immediately upon standing. The control periods varied widely; all hospitalized patients were observed at least one week prior to administration of the drug, and all measurements of blood pressure were recorded in the calculations. Outpatients usually had been followed for one to four years at intervals of two to three months. Placebos resembling the drug exactly were substituted for it without the patient's knowledge unless there was no doubt that the effects observed were real and not psychogenic (in the more severe cases, for example). Hospitalized patients were not informed that the drug was given for hypertension.

All blood pressure measurements were considered to be "casual" in the sense that no concerted attempt was made to obtain "basal" readings. Therefore the results were evaluated by including the highest and lowest single values recorded and the averages of all made during the pretreatment period, the period of administration of the drug, that of administration of a placebo, and subsequent periods. This method of analysis, while severe, permitted comparisons of extremes as well as of means. Decline of average diastolic pressure of 20 mm. Hg or more from control values was considered a significant change.

1-Hydrazinophthalazine (C-5968) and a derivative, 4-methyl-1-hydrazinophthalazine (C-6130) were administered in doses of 50 to 150 mg. every four to six hours in hospitalized patients, and three to five times a day to outpatients. Variability of individual tolerance was encountered early in the study, the extremes of dosage being 75 to 900 mg. per day. No attempt was made to give more than 900 mg. All drugs were given by mouth.

The additive effect of the drug with other forms of therapy, such as lumbodorsal sympathectomy and restriction of sodium chloride, was evaluated in nine patients. Any regimen on which the patient had been placed was not changed during administration of the drug. In two instances Veriloid was used in conjunction with C-5968. No sedatives were employed.

There were several purposes for the present study. First, the antihypertensive properties of the drug and its limits were investigated. Relatively short periods of administration in hospital (10 to 30 days) were adequate to decide whether or not blood pressure could be maintained at lower levels without deleterious renal, cardiac or cerebral effects. Second, the toxicity and side action were evaluated. Third, the action following lumbodorsal sympathectomy and with other forms of therapy was studied, again requiring relatively short periods of observation. Fourth, a practical clinical experience with outpatients was obtained in order to assess long-term therapeutic possibilities; daily observations of a few patients for three to eight months were made.

Results

1. *Antihypertensive Properties.* Significant sustained lowering of diastolic pressure of 20 mm. Hg or more occurred during administration of 1-hydrazinophthalazine in 6 of 16 patients observed in hospital. All of these patients were suffering from uncomplicated arterial hypertension in the benign phase. In four the average change was more than 30 mm. Renal function as measured by the excretion of phenol red or the clearance of urea was not depressed. In no case were strictly normotensive levels maintained. In five other patients average diastolic pressure fell 15 mm. Hg or more.

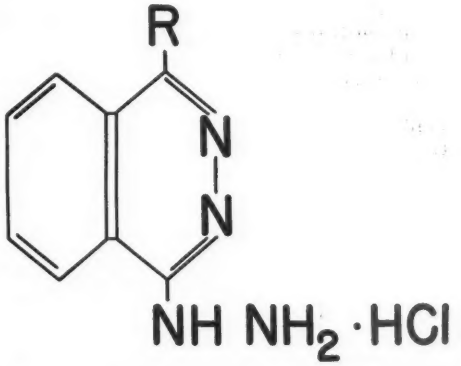

Fig. 1. Basic structure of 1-hydrazinophthalazine. In C-5968, R is hydrogen; in C-6130, R is a methyl group. Other derivatives untested so far in hypertension include those in which R is a hydrazine group.

In malignant hypertension without nitrogen retention the drug appeared to have a more pronounced action than in severe benign hypertension. Given to three patients, it lowered diastolic pressure considerably, and these lower levels were maintained as long as it was given. Occasionally, relatively acute and severe depression was followed by what seemed to be tolerance, blood pressure then being maintained at levels lower than those of the control period but considerably higher than the lowest values reached. Malignant hypertension with uremia (six cases) was also remarkably susceptible to the action of the drug. In two instances patients who were mentally depressed became comatose as the blood pressure fell and in two others neurotic episodes developed.

The combined results are given in table 1. Albuminuria diminished or disappeared in 14 of 15 patients. Adverse electrocardiographic changes were not evident; paroxysmal nocturnal dyspnea was relieved in three patients without the use of digitalis. Regression of hemorrhages, exudates and papilledema in the ocular fundi occurred in four instances, but could not be attributed directly to the action of the drug. Little or no action was demonstrated in two patients with hypertension secondary to chronic glomerulonephritis and in three with congestive heart failure. In fact, blood pressure tended to rise in a case of the former, the only time an adverse effect was noticed.

2. *Toxic Reactions.* No serious chronic toxic manifestations were encountered in patients receiving 1-hydrazinophthalazine for periods of as long as eight months. These studies are continuing. Depression of red or white blood cells, evidence of renal damage, chronic gastrointestinal disturbances, or other severe manifestations were not seen. Careful studies of liver function were not made, as no patient presented symptoms suggestive of liver disorder. Electrocardiographic abnormalities were not found.

Side reactions to the drug were seen on first administration in 22 of 50 patients. Headache, of the type commonly experienced as a symptom of hypertension, was induced by the first

TABLE 1.—*Effect of C-5968 on Various Types of Hypertension*

Type of Hypertension	No. Cases	Fall of Average Diastolic Pressure mm. Hg				Albuminuria		P.S.P. Excretion in 15 minutes†		Time Administered No. Patients/Weeks
		30	21–30	11–20	11	No. Cases Studied	No. Improved	No. Cases Studied	No. Decreased	
Hospital Patients										
Benign Uncomplicated	16	4	2	5	5	2	2	1	0	6/1, 6/2, 2/4, 1/7, 1/9
Malignant										
Without N retention	3	2	1	—	—	2	2	2	0	2/1, 1/7
With N retention	6	3	3			5	5	2	0	4/2, 1/3, 1/13
Postsympathectomy	7	2	5			2	2	1	0	2/2, 1/3, 2/5, 1/13, 1/31
Cardiac Failure	3			1	2	1	1	1	0	1/1, 2/2
Glomerulonephritis	2				2	1	0	—	—	1/1, 1/2
Pyelonephritis	2			2		—	—	—	—	1/2, 1/4
Arteriosclerosis	3			2	1	—	—	—	—	2/1, 1/4
Outpatients	15									
Benign Uncomplicated	12	1	9	2		2	2	1	0	4/1, 1/2, 1/4, 1/9, 2/13, 1/19, 1/23, 1/31, 1/33
Postsympathectomy	3	1	2			—	—	—	—	1/11, 1/13, 1/31
Totals	57*	13	22	12	10	15	14	8	0	

* Seven cases were seen both in hospital and as outpatients.

† After intravenous injection.

TABLE 2.—*Toxicity and Side Actions of C-5968 in Fifty Patients*

Symptom	No. Times Encountered	No. Times Disappeared On Continuing Drug
Postural Hypotension	45	38*
Headache		
Mild	8	8
Moderate	4	4
Severe	10	6
Nausea and Vomiting	11	9
Tachycardia	50	50
Angina Pectoris	1	0
Cerebral Symptoms	7	5
Numbness and Tingling of Extremities	4	0†

* Became less but did not disappear.

† Disappeared in a few days on discontinuing drug.

few doses in 22 subjects, and was severe enough to cause discontinuance in four. The headache was frequently controlled by Dramamine. Raising the level of dosage appeared to cause headache to recur. If the drug was continued, the headache disappeared in all but four cases (table 2) within two to five days.

Tachycardia was common during the first few days, disappearing as the drug was continued. Postural hypotension, which might be marked at first, regressed considerably but remained during the administration. Nausea and vomiting were present in 11 cases, also disappearing in a day or two in nine.

When hypertension was severe, cerebral symptoms often accompanied the fall in blood pressure, usually disappearing later. These ranged from mild anxiety or depression, to acute anxiety states or severe depression and coma. They occurred in seven subjects, regressing in all but two who were severely uremic and who remained in coma.

3. *Combined Action with Other Forms of Therapy.* After lumbodorsal sympathectomy 1-hydrazinophthalazine was found to exert a much more pronounced effect than before the operation. Seven patients were studied. Postural hypotension became so marked that dizziness in the upright position could readily be induced. The effects upon supine blood pressure were variable. During the month after operation, when the blood pressure had risen to relatively high values, normotensive levels could be continuously maintained in two subjects. In the remainder, who had had relatively unsuccessful sympathectomies one to four years previously, the effect was often considerable; standing blood pressure could be maintained at normal levels, although that in the supine position remained moderately elevated.

The drug was given to two patients who were on diets severely restricted as to salt. The results were quite favorable, and indicated increased susceptibility during salt restriction or rice diet. Veriloid was added to C-5968 in two cases; temporary but not sustained hypotensive levels were obtained. The combination of C-5968 with Priscoline or Regitine did not result in enhancement of the effect of either.

4. *Clinical Trial on Outpatients.* Fifteen patients suffering from benign arterial hypertension of various degrees of severity were given C-5968 or C-6130 for one to eight months; blood pressures, reclining and standing, were recorded six days a week. Placebos or no medication were given for short periods. Three patients refused the drug after three days because of headache, dizziness and faintness; all were in mild stages of the disease. Five others gave up the medication voluntarily after 2 to 10

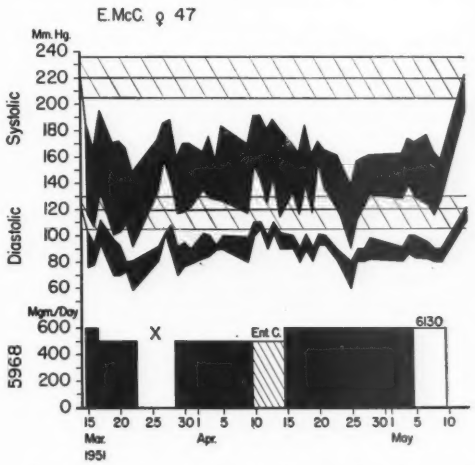

FIG. 2. Curve of average blood pressure of E. M., a 41 year old woman with severe hypertension unrelieved by sympathectomy three years previously. The crosshatched areas represent the extremes of systolic and diastolic pressure recorded during the entire observation of the patient prior to therapy with C-5968 with the exception of the immediate postoperative period; the horizontal lines are the average levels for this period. The shaded areas represent the postural fall in the erect position. Placebo administration is indicated by an X, the administration of enteric coated capsules by Ent. C., C-5968 by the solid blocks, and C-6130 by the open block. All readings were made on an outpatient basis.

weeks, usually because of the difficulty of making daily visits. Seven continued to accept treatment and three became dependent upon it. The results are shown in table 1 and figures 2 and 3.

The actions of C-5968 and C-6130 were compared in 10 subjects. No differences were detectable by these studies. Enteric coated tablets of the C-5968, given to six patients, either caused effects similar to those seen with ad-

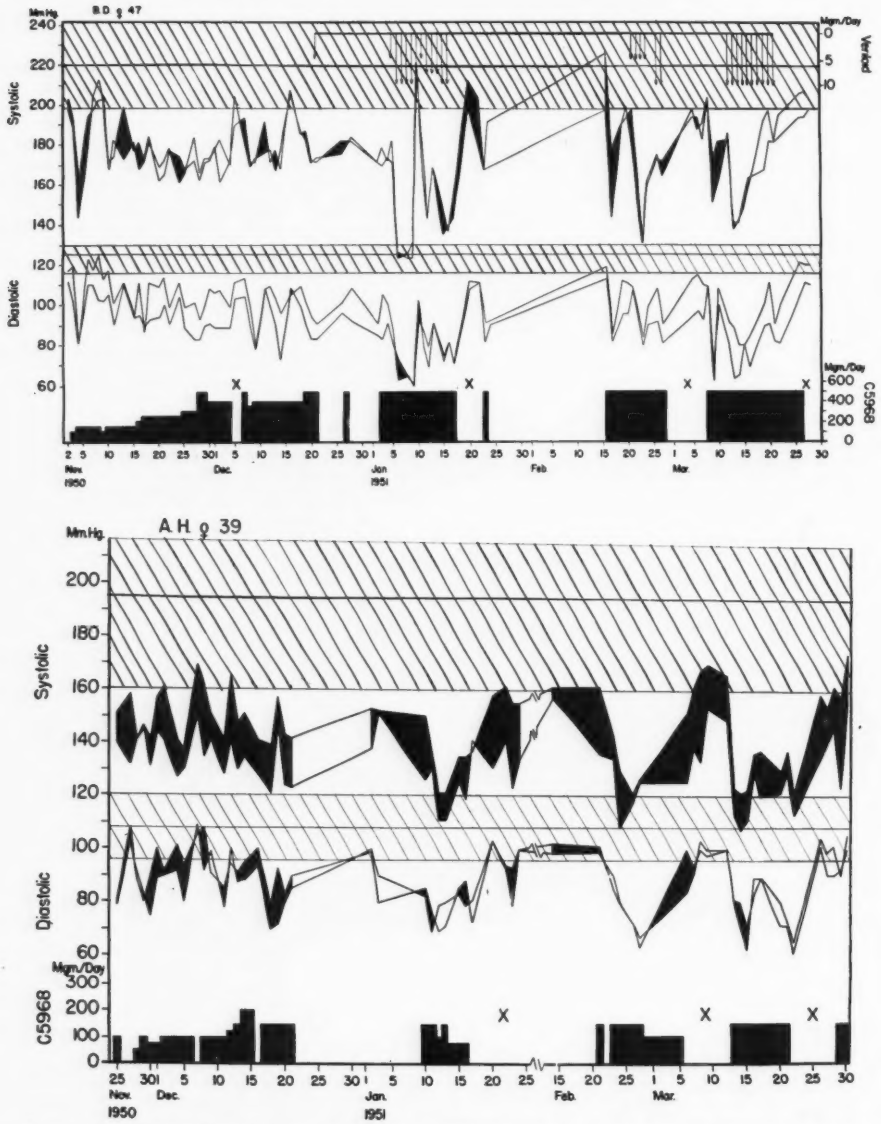

FIG. 3. *A*. (Upper Chart) Effect of 1-hydrazinophthalazine in a 47 year old Negro woman with moderately severe benign hypertension of the endocrine type. Notations same as figure 2. Albuminuria of slight degree disappeared two weeks after therapy was begun but reappeared when it was stopped, only to disappear again on resumption of therapy. Renal function was not disturbed from low normal levels. Headache of moderate intensity disappeared. When minimal doses of Veriloid were given in addition, marked unsustained lowering of blood pressure occurred. Note the relatively small postural fall of systolic pressure and the rise of diastolic, indicated by the absence of shading. The control areas represent three years' observation.

B. (Lower Chart) Same in a 39 year old Negro woman with relatively mild hypertension. The postural systolic fall was greater, and lower levels were sustained which were sometimes at normal levels. Normal renal and cardiac function were unchanged. The control areas represent three years observation.

ministration of placebos or produced only minimal changes in blood pressure.

5. *Comparative Effects in Different Types of Hypertension.* Patients were classified according to methods and criteria previously described[12] and the effects of the drug evaluated in each type. In general, it appeared that the most pronounced effects occurred in neurogenic hypertension, some cases of malignant hypertension and those who had had lumbodorsal sympathectomy; minimal changes were seen in severe renal hypertension with good renal function. A comparison of the relative effectiveness of C-5968 is shown in figures 4 to 8.

Discussion

The pharmacology of 1-hydrazinophthalazine and 4-methyl-1-hydrazinophthalazine is shown, in so far as is known, in table 3. It is obvious that these compounds have actions of a type not enjoyed by other known depressor agents. Evidence for a "sympatholytic" nature is equivocal and apparently dependent upon dosage and species. The site of action is not known; the blood pressure of "spinal" cats and dogs is not lowered by the drugs, suggesting an action on the vasomotor centers or hypothalamus.[4] However, they may be considered autonomic blocking agents of a special and hitherto undescribed type, as evidenced by their ability to inhibit the pressor response to pain (cold pressor test) and to the Valsalva maneuver. The effects are not due to sedation, not due to direct action on smooth muscle, and are not primarily peripheral.[13]

The action of these drugs on blood pressure and renal blood flow are of paramount importance to the problem of hypertension. Any substance which lowers blood pressure without causing diminution of renal blood flow is of interest. The present drugs apparently exhibit just this action. Being relatively nontoxic, they can be administered for several months to patients suffering from arterial hypertension of certain types and varieties with the expectation that the blood pressure will be lowered without deleterious renal effects. It can be assumed that thereby some of the damage to the cardiovascular system resulting from sustained high arterial pressure may be partially prevented. There is little evidence, however, that the present investigation represents much more than a therapeutic *tour de force.* Convincing data that life was prolonged by the drug was present in only two patients in whom considerably diminished renal function, severe retinitis, and severe hypertension all regressed remarkably after two to three months' treatment. Several years of continuous therapy in a large number

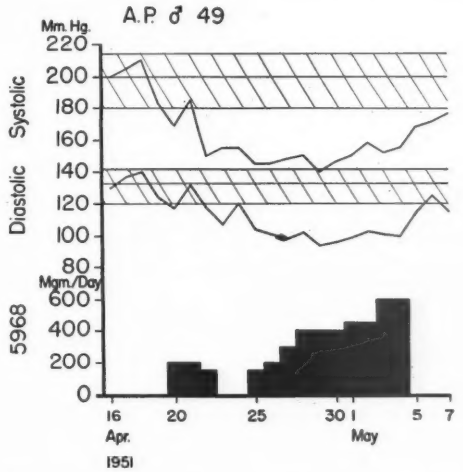

Fig. 4. Typical acute response of the average blood pressure in malignant hypertension to the administration of 1-hydrazinophthalazine. A. P. was a 49 year old engineer with severe, relatively acute malignant hypertension of one months' duration engrafted upon an elevated blood pressure for five years. The nonprotein nitrogen in his blood was slightly elevated, his renal function severely depressed (PSP less than 5 per cent excreted in 15 minutes) and there was 3 plus albuminuria. He was totally blind in his left eye, partially so in his right, due apparently to papilledema and marked hemorrhagic and exudative lesions in his ocular fundi. Subsequent to the period shown continuous therapy was instituted for two months; his blood pressure remained at slightly elevated levels, his vision partly returned, his albuminuria diminished and his renal function became more normal (PSP 15 per cent excreted in 15 minutes). Observations were made in hospital.

of patients may be necessary to evaluate long-term benefits, if any.

Although no chronic toxic manifestations were observed, undoubtedly some will appear with wider use of these drugs. It will then be

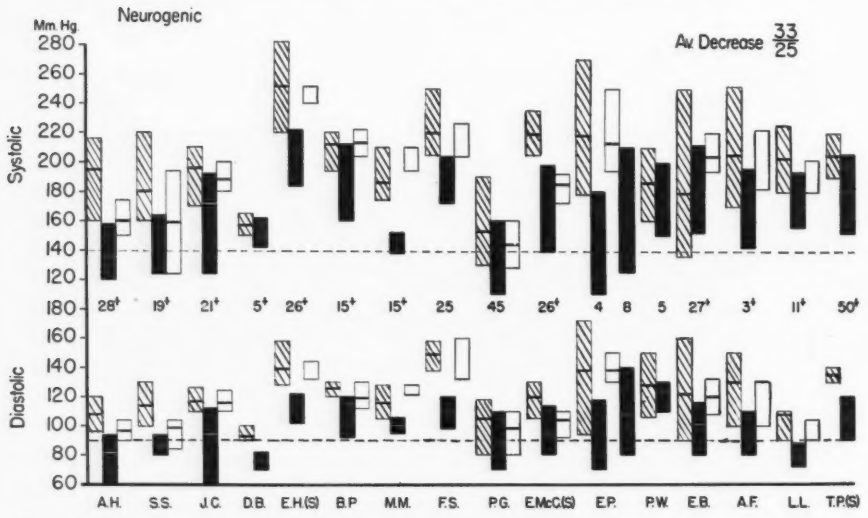

FIG. 5. Effect of 1-hydrazinophthalazine in neurogenic hypertension. The bars represent the extremes of systolic and diastolic pressure, the horizontal lines through them the means. The cross-hatched bars indicate the control periods, and include all measurements recorded up to four years prior to therapy. The solid bars indicate the periods of treatment, and the open bars those during which a placebo or no medication was given subsequent to treatment. The numbers show the number of days of therapy from which the blood pressure measurements were taken; a plus sign indicates outpatients. (S) after the initials in the bottom row means that the patient has had lumbodorsal sympathectomy. All measurements were made in the supine position. Note the relatively good response in most of the members of this group, except D.B. and E.B.

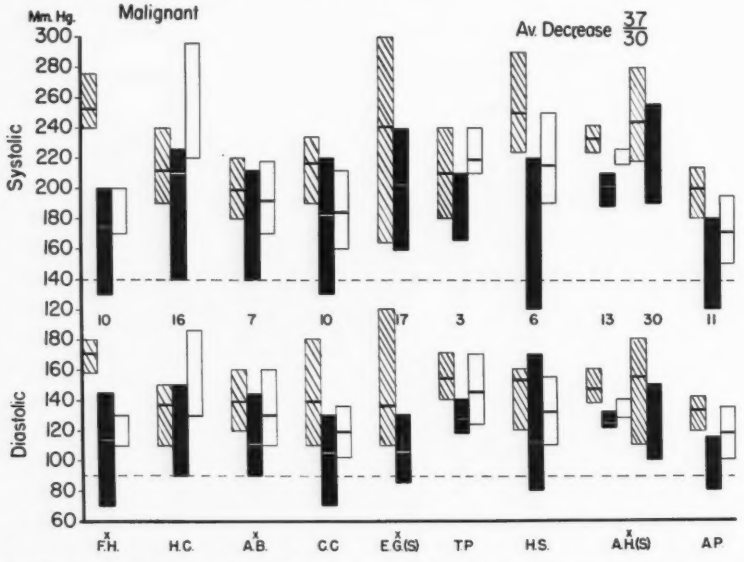

FIG. 6. Effect of 1-hydrazinophthalazine in malignant hypertension. Notations same as figure 5. The X above the initials indicates that the patient died during observation. Note the relatively good response in this group, with the exception of A.H., who died of a cerebral hemorrhage during treatment; his blood pressure while standing was controlled at normal levels, but when supine it remained high. All measurements were made in the supine position in hospital.

necessary to assess them against possible therapeutic value. In almost every case foreign unnatural chemicals introduced into the human body have resulted in toxic reactions. Evidence for this drug resembling a naturally occurring substance is lacking.

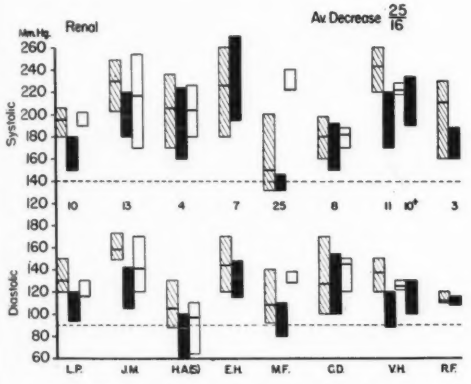

FIG. 7. Effect of 1-hydrazinophthalazine in renal hypertension; the group included those with nephrosclerosis as well as those with organic renal diseases. Notations same as figure 5. Note the relatively poor response in all but L. P., and V. H.

The side actions of these drugs are usually not serious enough to contraindicate a therapeutic trial. The headache, which may be severe, is probably not due to direct action of the drugs, but may be an indirect result of the lowered blood pressure and may be caused by the release of histamine. Typical headaches can be induced both by the drugs and by histamine, may be accompanied by stuffiness of the nose, watering of the eyes, and injection of the conjunctivae and can often be relieved by antihistaminic agents. The fact that they usually disappear while the drugs are being given is good evidence against their being drug-induced. Tachycardia and postural hypotension may also diminish as blood pressure becomes stabilized at lower levels, although the latter usually persists in mild degree; these are probably direct actions of the drugs. Nausea, vomiting and the occasional abdominal cramps and desire for defecation experienced by a few individuals may represent signs of autonomic imbalance induced by the drugs, especially as their symptoms were seen more often in patients who had been subjected to sympathec-

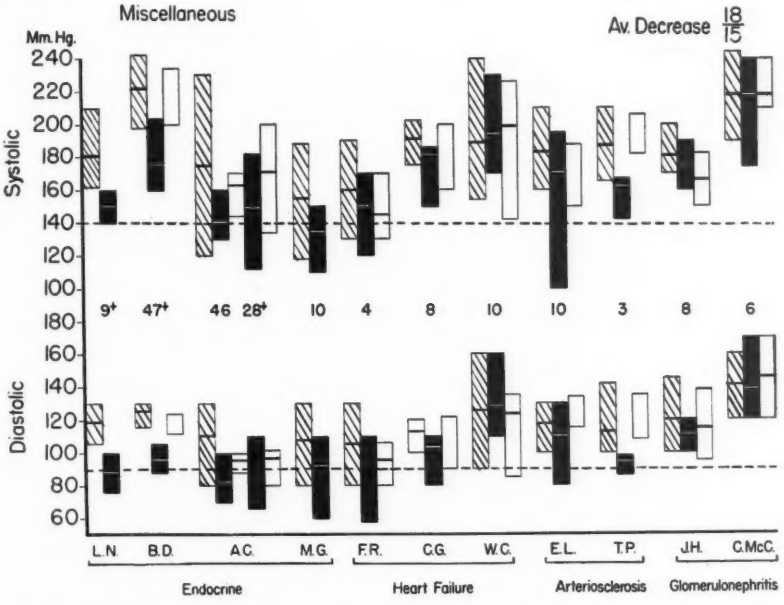

FIG. 8. Effect of 1-hydrazinophthalazine in miscellaneous types of hypertension. Notations same as figure 5. The response in the three with cardiac failure, the two with glomerulonephritis, and two of the four with the endocrine type is poor. This chart, and the preceding three, show individual data on 44 of the 50 patients treated. The remaining six were not charted but included in the tables.

tomy. The onset of angina pectoris in one individual was a serious complication, but one to be predicted when coronary arterial sclerosis is advanced but is compensated for by diastolic hypertension. Because of the occurrence of severe hypotensive episodes shortly after the beginning of treatment in two patients with considerably more effective shall the present study prove valuable. The treatment of renal hypertension remains unsolved.

Summary and Conclusions

Fifty patients suffering from arterial hypertension of various types were given 1-hydrazinophthalazine and/or 4-methyl-1-hydrazinophthalazine by mouth for periods of 1 to 40 weeks. Significant lowering of average diastolic blood pressure of 20 mm. Hg or more resulted in 35 instances, but in only a few of the mildest cases were normotensive levels sustained. The changes were not accompanied by deleterious effects upon kidneys or heart. These agents therefore represent true antihypertensive drugs of moderate potency.

Table 3.—*Pharmacologic Actions of 1-Hydrazinophthalazine and 4-Methyl-1-hydrazinophthalazine*

Function	Rat	Cat[4]	Dog	Rabbit[4]	Man
Blood Pressure	Reduced[4]	Reduced	Reduced[4, 7]	Reduced	Sl. Reduced[1, 3]
Hypertension	Reduced[5]		Reduced[5]		Reduced[5]
Respiratory Rate	No Effect[5]	Sl. Increase	No Effect[5]	Sl. Increased	No Effect[5]
Renal Blood Flow		Increased	Increased[4]		Increased[1]
					Filtration Fraction Decreased
Femoral Blood Flow		Increased	Increased[4]		
Digital Blood Flow					Increased[3]
Heart Rate	Increased[5]	Increased	Increased[4, 5, 7]	Increased	Increased Temporarily[1, 3, 5]
Isolated Heart					
Coronary Flow				Increased	No ECG Changes[5]
Amplitude		Decreased	No Effect[6]	Decreased	
Abolition of Pressor Response of:					
Epinephrine	Yes[4]	Yes	No[7]		No[3]
Norepinephrine		No	No[7]		Moderate[3]
Ephedrine		No			
Angiotonin	Yes[5, 8]				
Privine		No			
Pituitrin		No			
Valsalva "overshoot"					Yes[3]
Cold Pressor Test					Yes[3]
Response of Nictitating Membrane to Epinephrine		Diminished			
Smooth Muscle of Intestine			No Effect		
Respiration of Organ Slices	No Effect[6]	No Effect[6]			
Oral LD/100 Gm./Kg.	0.3			0.4	

Note: Numbers refer to references in bibliography.

malignant hypertension, it is our practice to initiate therapy slowly, with gradually increasing doses, preferably in hospital or, at the very least, under daily observation.

These two members of the hydrazinophthalazine group are the most effective agents against hypertension so far encountered for practical clinical use and represent true antihypertensive drugs. They do not, however, provide a therapeutic answer to this pressing problem; their effects are only partial. Only insofar as they may lead to further developments along the present line which will be

Acknowledgment

The author is indebted to Drs. William H. Stimson, Richard F. Huck, and Melvin L. Goldman for

their supervision of treatment of several patients; to Miss Julia E. Finn for preparation of the charts and data; and especially to Drs. F. F. Yonkman and F. L. Mohr of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for generous supplies of drugs, special preparations, and constant advice and cooperation during the past two years.

Addendum

Experience with this agent in an additional 20 patients has confirmed the present observations. No other evidences of chronic toxicity have appeared. In three cases, high fever without evidence of infection developed during administration of C-5968, regressing spontaneously; two of these patients had shown signs of previous cerebral damage. The fever was believed to be of central origin. Patients receiving this drug continuously for as long as 11 months have shown no signs of toxicity; blood counts and studies of liver function have remained normal. Tolerance to the drug has developed in several instances; discontinuance for a few days has restored susceptibility.

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The Effects of the Valsalva-like Maneuver upon the Circulation in Normal Individuals and Patients with Mitral Stenosis

By H. GOLDBERG, M.D., E. I. ELISBERG, M.D., AND L. N. KATZ, M.D.

A Valsalva-like maneuver was performed during cardiac catheterization by a normal group of individuals and a group of patients with acoustic evidence of mitral stenosis. The latter group was subdivided according to its response to the maneuver. The mild group, like the normal group, showed an "overshoot" of blood pressure and a bradycardia in the post-straining period, whereas the severe mitral stenosis group did not. The relatively undisturbed dynamics of the mild mitral stenosis group, in contrast to the marked disturbance in the severe group, was felt to be due to the amount of obstruction at the mitral valve. Additional data from the cardiac catheterizations of these patients is presented to substantiate this concept. This simple maneuver may prove to be a bedside method for the evaluation of the dynamic significance of mitral stenosis.

THE DYNAMIC effects of mitral stenosis have been the subject of many investigations. The circulatory disturbances produced by it have long been known, chiefly through animal experimentation.[1, 2] Recently, data accumulated by means of right heart catheterization have confirmed and expanded these observations.[3–7] Clinically, patients with mitral stenosis may be seen with little, if any, changes in their cardiovascular systems. With the possibility of surgical intervention, the need of assaying the magnitude of the stenosis has become obvious recently. This was recognized some years ago, when it was pointed out that the mitral valve area must be reduced at least 50 per cent in animals before its diverse effects upon the systemic circulation become evident.[1] Attempts have been made in man by elaborate formulas to arrive at a similar judgment.[8] The simple method of measuring the stenotic index suggested by this department for pulmonary stenosis[9] may also be applied to mitral stenosis.

In the course of a recent investigation of the relationship of respiration to cardiovascular dynamics, we studied the effects of a Valsalva-like maneuver upon the circulation. The response in patients with dynamically significant mitral stenosis was distinctly different from the response in patients with lesions of little or no dynamic significance and in normal individuals. These observations suggest that this Valsalva-like maneuver with certain simple measurements might be a useful adjunct in establishing the dynamic significance of a deformed mitral valve. The present report bears on this promising lead.

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. The department is supported in part by the Michael Reese Research Foundation.

Aided by a grant from the National Heart Institute (H 218C).

MATERIAL

The individuals comprising this study were selected from the Cardiac Clinic and Medical Wards of the Michael Reese Hospital. A complete history and physical examination was taken on each patient and examination by fluoroscopy, roentgenograms and electrocardiograms was included.

The individuals were divided into three groups: normal, mild mitral stenosis and severe mitral stenosis. The significant data are assembled in table 1.

1. *Normal.* Each of the three individuals in this group, cases 1, 2 and 3, 22, 26 and 34 years of age respectively, was considered to have a normal cardiorespiratory system.

2. *Mitral Stenosis (Mild), Group 1.* The three patients of this group had acoustic evidence of mitral stenosis. However, their resting pulmonary artery pressures, their response to exercise and to the Valsalva-like maneuver, showed that the mitral lesion had little effect on the cardiodynamics (table 1). These patients, cases 4, 5 and 6, 19, 30 and 35 years of age respectively, had known mitral lesions for one and one-half to five years. There were no known rheumatic episodes in childhood, though case

6 had joint symptoms one year prior to cardiac catheterization. Case 5 had a mitral valvulotomy several months before the postoperative catheterization reported here. Case 4 was completely symptom free, cases 5 and 6 showed dyspnea only on prolonged exertion. (In case 5 there was a considerable improvement from his clinical state before valvulotomy.) All patients had acoustic evidence of mitral stenosis, and case 4 had, in addition, acoustic evidence of mitral insufficiency and aortic regurgitation. Cases 4 and 5 showed only left auricular enlargement on fluoroscopy. In addition to this, case 6 showed slight enlargement of the outflow tract of the right ventricle. The electrocardiograms in this group were within normal limits.

3. *Mitral Stenosis (Severe), Group 2.* The four patients of this group, cases 7, 8, 9 and 10, 22, 23, 33 and 39 years of age respectively, had mitral disease with evidence in their resting pulmonary artery pressures and in their response to exercise and to the Valsalva-like maneuver which suggested a valve lesion severe enough to have led to demonstrable cardiodynamic alterations (table 1). Cases 8, 9 and 10 had had known episodes of rheumatic fever in childhood, and case 7 was known to have mitral stenosis for four years. Cases 8 and 9 had dyspnea on moderate exertion. Cases 7 and 10 had had episodes of congestive heart failure, and were dyspneic on slight exertion. However, none of these patients was in congestive heart failure at the time of this study. Acoustic evidence of mitral stenosis was present in all cases. In addition, case 9 showed acoustic evidence of aortic valvular deformity. Fluoroscopy revealed gross cardiac enlargement, including left auricular enlargement, except in case 10 in which there was only left auricular enlargement (the right ventricular outflow tract being at the upper limits of normal). Cases 8 and 9 had auricular fibrillation. The electrocardiograms in all these patients were definitely abnormal. Cases 7, 8 and 9 were taking digitoxin.

Method

All studies were done in the Florsheim Cardiovascular X-ray Research Unit in the morning without prior sedation. Under local anesthesia (Metycaine) a Cournand needle was placed in the brachial artery of the left arm for data on systemic arterial oxygen and pressure. Cardiac catheterization was performed according to the technic of Cournand and Ranges.[10] The catheter was placed in the pulmonary artery in all instances except in case 3 in which it could not be advanced beyond the right ventricle. Simultaneous pressure tracings from the pulmonary artery (or right ventricle) and brachial artery, using electromanometers* recording on a four channel direct-writing polyoscillograph,* were made together with lead II of the electrocardiogram.

* Sanborn Company, Cambridge, Massachusetts.

After a short control tracing, the patient was instructed to blow into a mercury manometer for as long as he was able, a Valsalva-like maneuver. Maximum sustained intraoral pressure was recorded by the method recently described.[11] Afterward the patient relaxed. Continuous tracings were made until the pressure in the pulmonary and brachial arteries had returned to normal.

The effect of the Valsalva-like procedure on the circulation was divided into four phases as suggested by Hamilton.[12] The first phase occurs immediately after straining begins, the second during the course of the sustained straining, the third immediately after straining ends, and the fourth lasts until blood pressure reaches control levels. Tabulation of the systolic, diastolic, and pulse pressures and of the heart rate during each of the four phases of the Valsalva-like maneuver was made in the systemic and pulmonary circuit in the normal as well as in the two groups of mitral cases and the results are summarized in table 1.

Results

1. *Effect of Straining on the Systemic Circulation and Heart Rate* (table 1, figs. 1, 2 and 4)

A. *Normal.* The Valsalva-like maneuver affected the systemic blood pressure, the contour of the pulse and the cardiac rate.

The average intraoral pressure for this normal group during the Valsalva-like maneuver was 55 mm. Hg, indicating that the average intrapleural pressure was about 48 mm. Hg.[11] Pressures in the pulmonary artery or right ventricle were normal at rest. They were also normal on exercise, when measured. The cardiac index at rest was in the accepted normal range in two patients and somewhat above this rate in one due to anxiety. In one of the two patients in whom exercise was done the cardiac index doubled. In the other case, the patient, a normal, healthy Mexican male, apparently had considerable anxiety at rest, with a resultant cardiac output of 10 liters per minute, and a cardiac index of 6.1 liters per minute per square meter of body surface. During exercise there was no appreciable change in the cardiac output. Dexter and coworkers[13] have published similar data on patients with a relatively high output at rest and Hickam and his associates[14] have actually shown a fall of cardiac output during cardiac catheterization when exercise was performed in normal anxious patients.

TABLE 1.—*Summary of Data on the Valsalva-like Maneuver Compared with Pertinent Cardiac Catheterization Findings*

Case	Brachial Artery															Pulmonary Artery										IOP	ECG	CI REST	CI EX.	PA REST	PA EX.
	Control			Phase 1			Phase 2			Phase 3			Phase 4			Control		Phase 1		Phase 2		Phase 3		Phase 4								
	BP	PP	R	BP	PP	R	BP	PP	R	BP	PP	R	BP	PP	R	BP	PP	BP	PP	BP	PP	BP	PP	BP	PP						
Normal																															
1.	128/64	64	75	164/106	58	75	128/96	32	94	70/48	22	107	156/86	70	54	22/10*	12	83/70	13	75/68	7	14/6	8	30/14	16	85	PWNL	6.1	6.0	24/9	26/11
2	132/84	48	83	152/106	46	83	78/74	4	107	50/46	4	136	222/134	88	60	14/4*	10	40/36	4	36/32	4	8/0	8	27/15	12	45	WNL	2.9	6.0	16/6	20/10
3	100/64	36	83	116/80	36	83	96/74	22	107	86/64	22	107	140/86	56	71	20/0†	20	40/18	22	32/13	18	17/0	17	30/0	30	35	WNL	3.78	—	22/0†	—
Av.	120/71	49	80	144/97	47	80	101/81	20	103	69/53	16	117	173/102	71	62	18/7*	11*	62/53*	9*	55/50*	5*	11/3*	8*	29/15*	14*	55	—	4.3/4.5*	6.0*	20/8*	23/11*
Mitral Stenosis (Mild) Group 1																															
4.	116/60	56	79	146/78	68	59	110/80	30	120	88/50	38	120	150/80	70	68	16/5	11	36/30	6	32/27	5	16/4	12	20/8	12	—	WNL	3.1	5.4	16-23/5-13	28-32/12-14
5.	110/70	40	81	144/96	48	58	130/100	30	88	100/76	24	94	136/80	56	60	31/16	15	48/40	8	43/34	9	16/8	8	38/20	18	—	WNL	2.6	3.3	35/15	40/25
6.	110/64	46	65	124/84	40	65	126/100	26	75	100/76	24	75	134/80	54	68	25/8	17	42/30	12	48/40	8	12/–5	17	39/20	19	50	WNL	2.1	4.2	28/10	39/13
Av.	112/65	47	75	138/86	52	61	122/93	29	94	96/67	29	96	140/80	60	65	24/10	14	42/33	9	41/34	7	15/2	12	32/16	16	—	—	2.6	4.0	31/11	36/17
Mitral Stenosis (Severe) Group 2																															
7.	98/62	36	83	118/84	34	83	110/80	30	83	86/58	28	88	100/64	36	88	67/28	39	81/49	32	70/50	20	50/25	25	70/30	40	50	RHS	2.7	—	67-83/28	—
8.	148/79	69	83	166/106	60	68	138/109	29	88	120/68	52	88	132/80	52	93	56/30	26	108/80	28	92/80	12	44/20	24	80/34	46	58	RHS A.F.	2.2	2.6	56/29	114/64
9.	165/97	68	103	184/114	70	88	171/110	61	103	154/100	54	103	164/96	68	105	59/24	35	86/57	29	67/43	24	58/22	36	68/30	38	66	RBBSB A.F.	4.4	4.4	59-64/24-35	93/38
10.	93/64	29	97	116/84	32	97	76/64	12	103	60/56	4	107	98/67	31	100	49/25	24	70/52	18	40/36	4	40/15	25	61/38	23	37	B.C. M.P.	2.6	3.0	49/25	92/50
Av.	126/76	50	91	146/97	49	84	124/91	33	94	105/71	34	97	124/77	47	97	58/27	31	86/59	27	67/52	15	48/21	27	70/33	37	53/54‡	—	3.0/3.1‡	3.3‡	61/28-56/26‡	100/51‡

* = Cases with pulmonary artery pressure
† = Cases with right ventricular pressure
‡ = Last 3 cases
BP = Blood pressure, mm. Hg
PP = Pulse pressure, mm. Hg
R = Cardiac rate, beats/min.

IOP = Intraoral pressure, mm. Hg
ECG = Electrocardiogram
CI = Cardiac index, L/min./M.²
PA = Pulmonary artery pressure, mm. Hg
EX. = Exercise
WNL = Within normal limits
PWNL = Probably within normal limits

RHS = Right heart strain
RBBSB = Right bundle branch system block
A.F. = Auricular fibrillation
B.C. = Borderline curve
M.P. = Mitral P waves

Data presented are averages of each phase.

Phase 1. With the onset of straining, both the systolic and diastolic blood pressures rose in all three patients while the pulse pressure remained close to the control value. The maximum pressure was attained very shortly after the straining was begun (within 4 beats). During this period the cardiac rate and pulse contour remained unchanged.

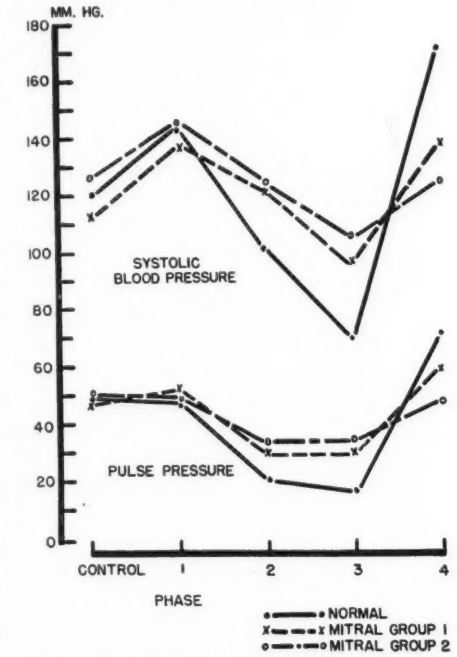

FIG. 1. Systolic blood pressure and pulse pressure recorded from the brachial artery during the control period and the four phases of the Valsalva-like maneuver, for normal subjects and for patients with mitral stenosis (mild), group 1, and (severe), group 2. Note the lack of "overshoot" in phase 4 in patients with mitral stenosis, group 2.

Phase 2. As the straining was sustained there was a gradual fall in the systolic and diastolic blood pressure, the former declining more than the latter. Consequently there was a decrease in pulse pressure. The latter became almost imperceptible in case 2. The systolic pressure in one instance fell below, and in two instances was at or near, the control level. In two instances the diastolic pressure remained above, and in one it fell below, the control level. The cardiac rate, in all instances, rose above the

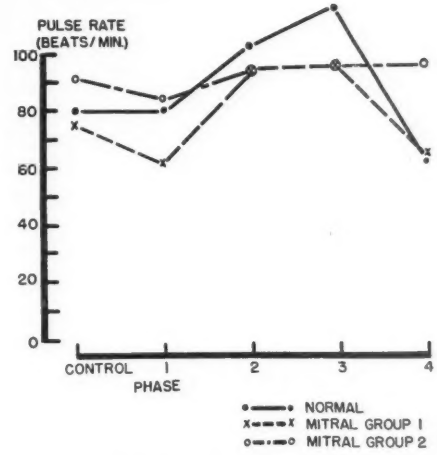

FIG. 2. Cardiac rate during the control period and four phases of the Valsalva-like maneuver for patients in normal group and in mitral stenosis, groups 1 and 2. Note relative constancy of pulse in severe mitral stenosis (group 2), and lack of bradycardia in phase 4 in this group.

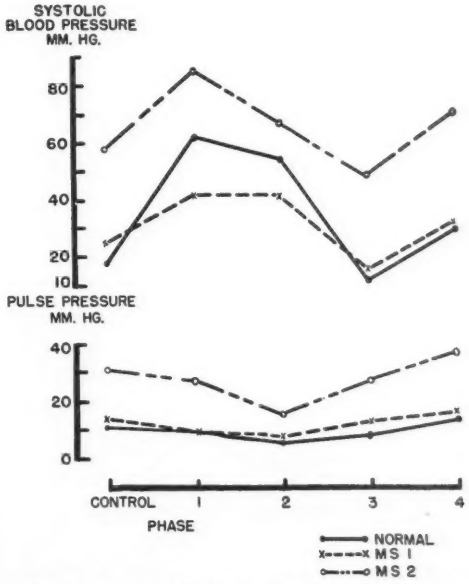

FIG. 3. Systolic blood pressure and pulse pressure as recorded from the pulmonary artery in normal subjects and mitral stenosis, groups 1 and 2, during the control period and four phases of a Valsalva-like maneuver. Note "overshoot" in all groups in phase 4 and that this is not as marked for each group as in the systemic circuit (compare with figure 1).

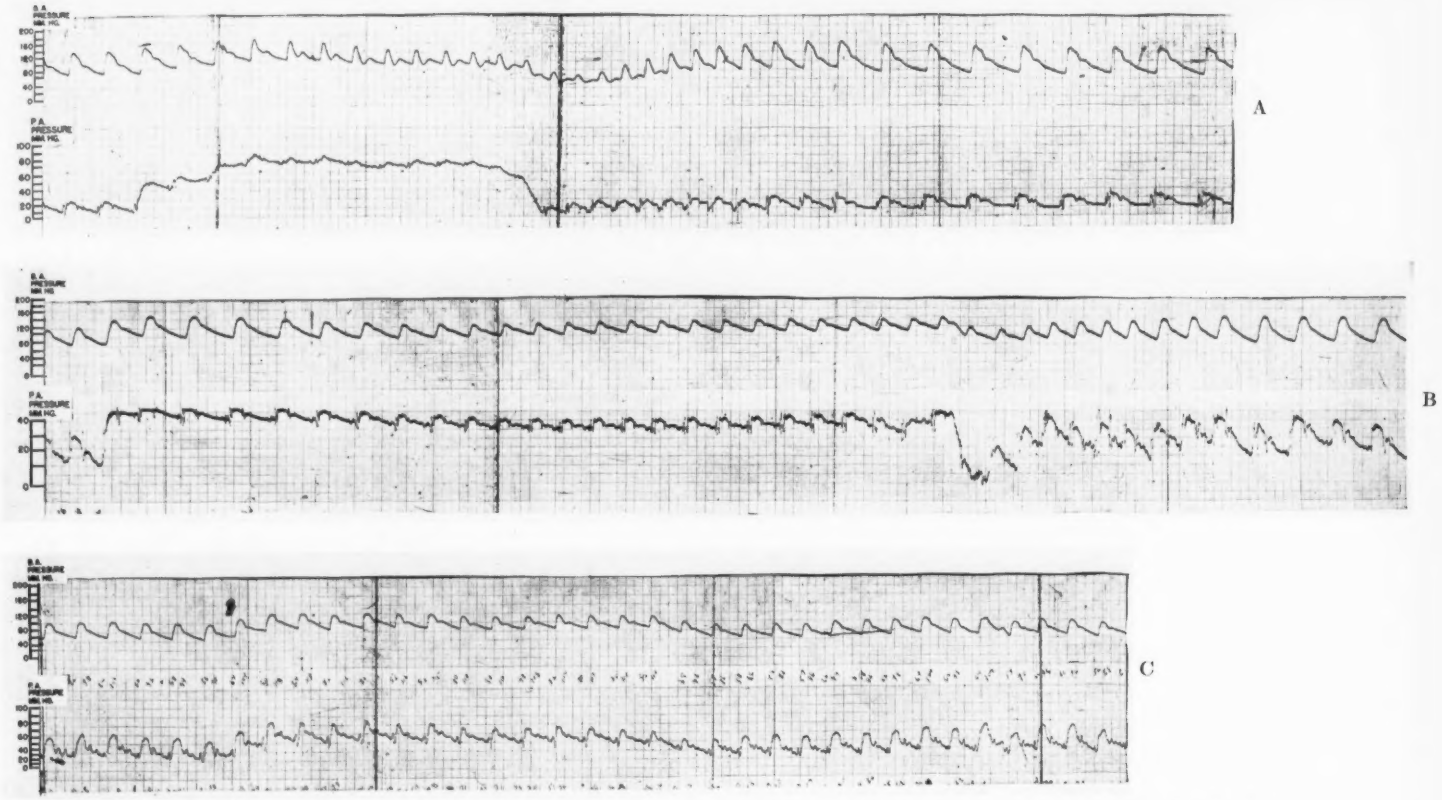

FIG. 4. Typical pressure records obtained with Valsalva-like maneuver from simultaneously registered brachial (upper) and pulmonary (lower) arteries. *A* is case 1, a normal individual; *B* is case 5, a patient with mild mitral stenosis (group 1); and *C* is case 7, a patient with severe mitral stenosis (group 2).

In the pressure records the Valsalva-like maneuver begins with a rapid rise in pressure, and ends with a sudden fall. The control period in *A* is the first 2½ beats, in *B* the first 1½ beats and in *C* the first 6 beats. Phase 1 of the Valsalva-like maneuver is the first few beats after the onset of the pressure rise, phase 2 occurs during the steady level of the pressures, phase 3 is the first beat or two immediately after the end of the maneuver during which the pressure falls, and phase 4 occurs over the next 8 to 10 beats—with "overshoot" and bradycardia present in *A* and *B* at this time and not present in *C*. There are 2 premature systoles near the end of record *C*.

Ordinates are pressures in mm. Hg, and abscissas indicate time, each heavy line equaling 0.2 second. Discussed in text.

control rate. In two instances, a definite sinus tachycardia was present. The contour of the pulse was markedly changed. The dicrotic notch approached end diastole and eventually the dicrotic pressure equaled the end diastolic pressure. The pulse curve tended to become symmetric, with the anacrotic limb equal to the catacrotic limb.

Phase 3. With the cessation of straining there was an immediate drop in both systolic and diastolic pressures. The pulse pressure usually remained the same as in phase 2. The blood pressure in all instances fell below the control level. The contour of the pulse remained essentially similar to that in the preceding phase. The cardiac rate was somewhat faster than in the previous phase.

Phase 4. Soon after cessation of straining the systolic and diastolic blood pressure rose. There was a relatively greater increase in the former so that the pulse pressure increased rapidly. The control blood pressure level was quickly reached (within 5 to 8 beats). The pressure continued to rise so that the control systolic, diastolic and pulse pressures were definitely exceeded in all three patients. During this period, termed the "overshooting" phase,[12] the pressure may rise to extremely high levels, with the heart rate at the same time becoming moderately or markedly slowed. In all three of our patients the heart rate fell below the control levels. The contour of the pulse returned to normal somewhat more slowly than the pressure. The dicrotic notch appeared higher on the catacrotic limb until it eventually assumed its normal position.

B. *Mitral Stenosis (Mild), Group 1.* As stated above, this group has much in common with the normal group. Though the cardiac index was slightly below normal in all three patients, there was a normal response of the cardiac output to exercise. The pulmonary artery pressures at rest were at the upper limits of normal, and were increased only slightly by exercise. The intraoral pressure was recorded in only one instance (case 6). It was 50 mm. Hg during the Valsalva-like maneuver, indicating that the average intrapleural pressure was about 43 mm. Hg.

The four phases of the Valsalva-like maneuver showed essentially the same response in the systemic circulation as did the subjects composing the normal group. In phase 1, coincident with the increase in blood pressure, there was a decrease in pulse rate in two of the three patients. The "overshoot" and bradycardia in phase 4, while not as great as in those of the normal group, was definite.

C. *Mitral Stenosis (Severe), Group 2.* The patients in this group, with one exception (case 9), had low cardiac indexes at rest and all had fixed cardiac indexes on exercise. The pulmonary artery pressures, high at rest, became considerably increased during exercise. The average intraoral pressure during the Valsalva-like maneuver was 53 mm. Hg, indicating that the average intrapleural pressure was about 46 mm. Hg.

As in the normal group, the effect of straining upon the systemic circulation may be divided into four phases. With the onset of straining, the systolic and diastolic pressures rose, the maximum pressure being attained before the fourth beat in all cases. The pulse pressure remained close to control level. The cardiac rate slowed in two of the four patients during phase 1, but returned to essentially control rates during the other phases. As the strain was sustained (phase 2) the pressure fell somewhat below that observed in phase 1. Although the pulse pressure became smaller, it did not decrease to the extremes noted in the normal group, except in case 10. Similarly, the pulse contour did not exhibit the marked changes observed in the control group. The cardiac rate was close to control level in this phase.

With the release of straining (phase 3), both systolic and diastolic pressures fell to below control levels, but not to the extent seen in the normal group. The pulse pressure remained as in phase 2 and the cardiac rate was unchanged.

During recovery (phase 4) the blood pressure rose gradually, returning to normal levels within 4 to 9 beats. The contour of the pulse followed the recovery of the blood pressure. The pronounced "overshooting" of the blood pressure was not observed in any of the patients in this group. The marked slowing of the pulse was also not observed in any case. In no in-

cardia present in A and B at this time and not present in C. Discussed in text.
Ordinates are pressures in mm. Hg and abscissa indicate time, each heavy line equaling 0.2 second.

stance did the cardiac rate during this phase fall below control levels.

Except for phase 1, when there was slowing in two patients, the cardiac rate remained at approximately control levels during all phases of the Valsalva-like maneuver.

2. *The Effect of Straining on the Pulmonary Circulation* (table 1, figs. 3 and 4)

A. *Normal.* With the onset of the Valsalva-like maneuver (phase 1) the systolic and diastolic pressures in the pulmonary artery (or right ventricle) rose in all subjects. The pulse pressure remained at control level in two patients and below it in the third. As straining was maintained (phase 2) the blood pressure fell slightly below the preceding phase. In contrast to the systemic circulation, however, the systolic and diastolic pressures in the pulmonary artery (or right ventricle) remained considerably above control levels during phase 2. During this phase all pulse pressures were reduced below control values. As the strain was released, the pressure within the lesser circulation dropped precipitously to below control levels, though the pulse pressure quickly rose above that in the previous phase. During recovery (phase 4) the blood pressure rose quickly, returning to control levels somewhat earlier than in the systemic circuit. An "overshoot" with an increased pulse pressure was present in the pulmonary artery (or right ventricle) but the pressure change was not nearly as marked as that observed in the systemic circuit. In no case were the upper limits of normal values for the pulmonary artery (or right ventricular pressures) exceeded during this phase.

B. *Mitral Stenosis* (*Mild*), *Group 1.* The findings in this group were essentially similar to those of the normal group. The systolic and diastolic pressures in this group during the period of the "overshoot" (phase 4) in two of the three patients were definitely elevated above normal values for pulmonary artery pressure. However, the control pressures in this group, while within normal limits, were higher than in the normal group, so that the actual "overshoot" was quantitatively similar to that seen in the normal group.

C. *Mitral Stenosis* (*Severe*), *Group 2.* The quantitative findings were similar to those shown by the other groups. The control pressures were higher, and as a result the "overshoot" present in the pulmonary circulation (in contrast to its absence in the systemic circuit) reached higher levels than in the other groups.

Discussion

The pressures recorded from the brachial and pulmonary arteries are gross pressures during the straining procedure. While the diastolic brachial artery pressure and the systolic and diastolic pulmonary arteries pressures are elevated during the sustained period of straining, the net blood pressure in these vessels—obtained by subtracting the simultaneous intrapleural pressure from the gross blood pressure—was actually found to be reduced, in confirmation of the findings of Cournand and coworkers.[15] This is particularly well seen in phase 3 where the blood pressure falls precipitously below control values when the support of the intrapleural pressure is removed.

Our observations on the effect of the Valsalva-like maneuver upon the systemic circuit in normal subjects are in agreement with those of Hamilton and co-workers.[12] With the onset of straining, the intrapleural pressure rises. We have found[11] that during the Valsalva-like maneuver intraoral pressure curves closely simulate intrapleural pressure curves in contour and have concluded that the intraoral pressure is an accurate measure of intrapleural pressure during this maneuver, being on the average 6 to 7 mm. Hg higher than the latter. With the onset of straining the pressure in the brachial artery rises. This undoubtedly is related to an increased output of the left ventricle, as a result of the blood forced into it from the lungs. As the strain is sustained, the blood pressure level and particularly the pulse pressure in the systemic circuit fall. This is attributable to the depletion of the pulmonary blood reservoir which is squeezed out by the increased intrapleural pressure and prevented from refilling by the simultaneous decrease in venous return to the heart resulting from the same cause. During these phases, reflexes may come

into play. These may explain the slowing of the heart in some cases during phase 1, when there is a sudden increase in blood pressure, and the increase in the heart rate in phase 2. The tachycardia persists into phase 3.

During straining the venous pressure becomes markedly elevated[16] because of interference with venous return. With the cessation of straining and the sudden release of the elevated intrapleural pressure, the venous pressure, as expected, falls abruptly. This is associated with a marked and immediate increase in the venous return of blood to the heart from the blood stored in the veins during straining, which is facilitated by the hyperpnea following straining. It is this brisk augmentation in venous return that leads to the "overshoot" in the blood pressure in phase 4. This marked blood pressure "overshoot" in the systemic circuit in its turn leads reflexogenically to slowing of the heart and to a generalized vasodilatation. The cardioregulatory reflexes appear to originate in the receptors of the carotid sinus and aortic arch and their effect may be eliminated by various drugs.[17, 18]

The response to the straining procedure in the systemic circulation of patients with dynamically insignificant mitral stenosis was similar to that observed in normal individuals. In patients of this group the blood pressure "overshoot" and bradycardia of phase 4 were present and marked, but to a lesser degree than in normal subjects. This suggests that the factors which operate in the more severe mitral stenosis cases do so in these milder cases but to a lesser extent. In the patients with severe mitral stenosis the blood pressures "overshoot" and bradycardia of phase 4 was absent or minimal.

In the pulmonary circulation all groups of patients showed an "overshoot" of approximately the same degree in the post-straining period of the Valsalva-like maneuver (phase 4) regardless of the initial resting pulmonary artery pressure. This was unexpected on the assumption that in severe mitral stenosis the pulmonary vascular bed was reduced because of the marked pulmonary vascular engorgement. However, apparently the pulmonary bed is so large[19] and can be emptied sufficiently by straining even in patients with a tight mitral stenosis, that it can accommodate the added post-straining load as well as in the normal individual without an augmented blood pressure "overshoot" in phase 4 (or the distensibility is altered with mitral stenosis).

The differences in the systemic blood pressure "overshoot" and its associated bradycardia between the normal subjects and those with tight mitral stenosis is obviously due to the obstruction at the mitral orifice. The deformed valve causes an obstruction to the filling of the left ventricle which normally occurs almost entirely during early diastole (in the rapid inflow phase). The auricular systolic contribution ordinarily is of minor importance and equal to about 5 per cent of total filling. Mitral stenosis affects chiefly the rapid inflow phase of left ventricular filling.[20] In mild degrees of stenosis, as in our mitral stenosis group 1, the tendency to impairment of filling during rapid inflow is compensated adequately by the elevation of left auricular pressure and by an augmented auricular contraction. The result will be a dynamically unimportant lesion but one with acoustic characteristics. When, however, the obstruction becomes severe, as in our mitral stenosis group 2, these compensatory mechanisms are inadequate and filling is impaired. As a result the cardiac index at rest tends to be low. The obstruction at the mitral valve not only operates to prevent filling at rest but does so during exercise. Hence the cardiac output cannot increase to the same degree in patients with "tight" mitral valves as in normal individuals. In fact, the disparity between normal subjects and patients with severe mitral stenosis is much more marked during exercise than at rest as we and others[3, 5–7] have found. A similar situation prevails during the Valsalva-like maneuver. The sudden increase in the quantity of blood entering the right heart from the blood pooled in the veins during the early post-straining period, as a result of the release of the increased intrapleural pressure, cannot readily pass on into the left ventricle because of the stenotic mitral valve. Hence, the blood is accommodated for a time behind the mitral valve until in the course of time it drains away. This

limitation to the augmentation of left ventricular filling and output is dependent on the severity of the degree of mitral stenosis. It determines in turn the presence and magnitude of the systemic blood pressure "overshoot" and its accompanying reflexogenic bradycardia. In mitral stenosis group 1, where the stenosis is mild, as evidenced by the high normal pulmonary arterial pressure at rest and the almost normal response of the pulmonary artery pressure and cardiac index to exercise, there was exhibited a definite but less than normal "overshooting" in systemic blood pressure and bradycardia in phase 4. In the severe cases, mitral stenosis group 2, with resting pulmonary hypertension, marked augmentation of pulmonary arterial pressure and fixed cardiac indexes on exercise, there was exhibited little or no "overshooting" in systemic blood pressure and little or no slowing in pulse rate in phase 4.

Since the reflexogenic bradycardia after straining in mitral stenosis is dependent on the magnitude of the "overshoot" in systemic arterial pressure and this is in turn inversely related to the severity of the mitral stenosis, it is possible that the presence or absence of the bradycardia and its degree after a standardized Valsalva-like maneuver may be used as a simple bedside index of the dynamic severity of mitral stenosis. It is obvious that this needs further testing in mitral stenosis. Furthermore, other circumstances which prevent the ready redistribution of blood on and after straining will have to be tested as well. Such studies are under way.

Summary

1. The effect of the straining procedure upon the systemic and pulmonary circulations in normal individuals and patients with mitral stenosis of several grades is described.

2. The response of patients with severe mitral stenosis to this procedure differs from that of normal individuals and individuals in whom the mitral stenosis is only of acoustic significance. The difference is based upon the altered dynamics created by the stenotic mitral valve.

3. The value of this procedure in establishing the dynamic significance of mitral stenosis and in estimating the size of the mitral valve is indicated.

4. It is possible that the presence or absence of the reflexogenic post-straining bradycardia and its degree with a standardized Valsalva-like maneuver may be used as a clinical bedside index of the degree of mitral stenosis. Other factors which can have an effect similar to mitral stenosis are being examined.

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Epicardial Electrocardiograms Recorded in the Course of Seven Cases of Heart Surgery

By GEORGES J. CAROUSO, M. D., HENRI A. CHEVALIER, M. D., B. ISABELLE LATSCHA, M. D., AND JEAN LENÈGRE, M. D.

Thirty-eight direct electrocardiographic records have been obtained by applying an exploring electrode directly to the epicardium after incision of the pericardium in the case of seven patients subjected to thoracotomy for various forms of heart surgery. These cases include three individuals with the tetralogy of Fallot, one with mitral stenosis, one with coarctation of the aorta, one with probable pulmonary atresia and one with a patent ductus arteriosus. This exploration has permitted us to study the patterns obtained in different regions of the right and left ventricular epicardial surfaces in four patients with right ventricular hypertrophy, two patients with left ventricular hypertrophy, and one patient with a heart whose left ventricle–right ventricle ratio was probably little disturbed.

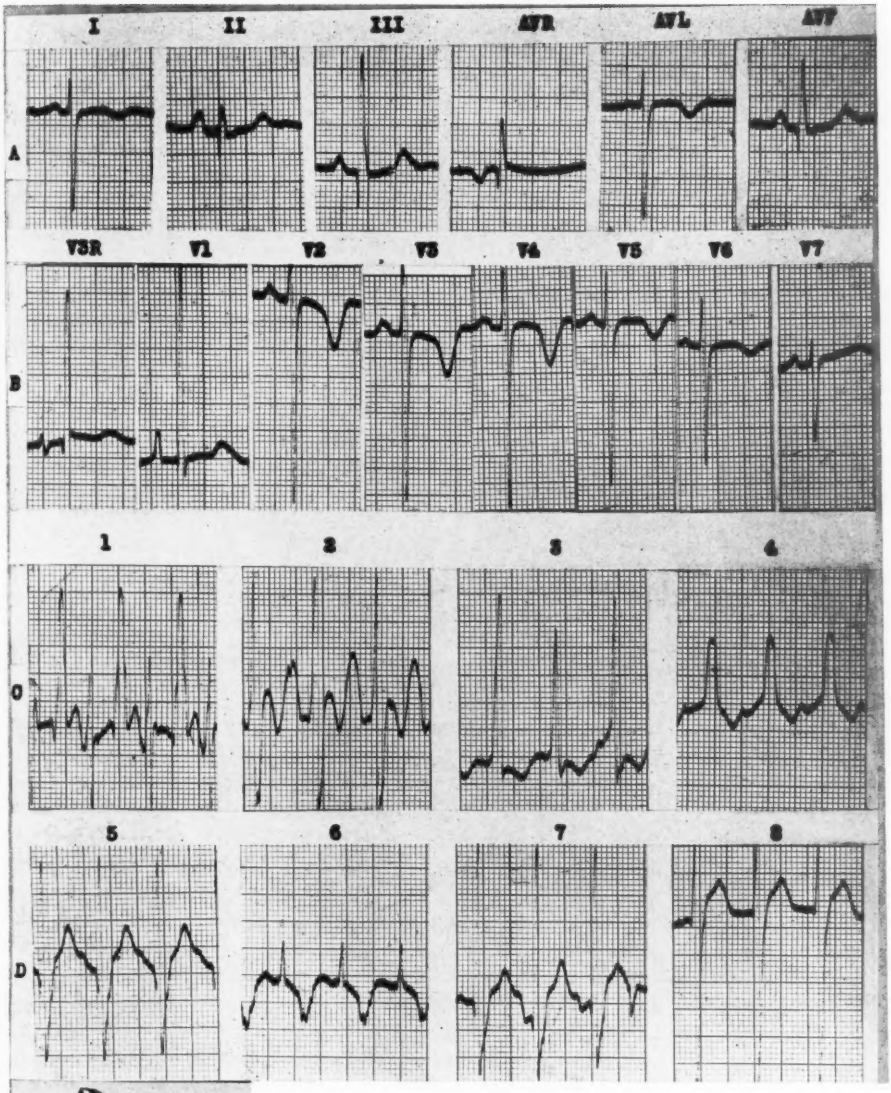
IT IS now well recognized that certain characteristic modifications of the QRS complex in unipolar precordial leads will result from right or left ventricular hypertrophy, respectively. However, there have not yet appeared any reports concerning the form of QRS in direct epicardial leads in such cases in man. Recently, we were afforded an opportunity to obtain such information in four instances of right ventricular hypertrophy (three due to tetralogy of Fallot and one to mitral stenosis) and in two instances of left ventricular hypertrophy (one due to a coarctation of the aorta and one due to an obscure type of anomaly associated with pulmonary atresia). In the present communication, it is our purpose to describe the findings thus obtained and to correlate the QRS pattern in direct epicardial leads with that in unipolar precordial leads in right and left ventricular hypertrophy, respectively.

METHOD

After the heart was exposed and the pericardium incised during operation for the treatment of the cardiovascular anomalies already described, direct unipolar leads were obtained by the application of an electrode directly upon various sites on the ventricular epicardium. The type of electrocardiograph available at the time of these studies did not permit the simultaneous registration of a lead on the body surface. The instrument was standardized to one-half of the usual sensitivity. The exploring electrode consisted of a polished silver disk measuring 13 mm. in diameter and 1 mm. in thickness. To one edge was attached a long handle, which facilitated its application. The disk was pliable and could be bent easily and made to conform to the cardiac surface being explored. This electrode could be introduced easily through the rent in the pericardium and could be held in contact with the visceral epicardium without the aid of absorbent cotton or other substance. The sites selected for the application of the exploring electrode were noted and charted, so that appropriate correlations could be made. Comparisons were then made in the same

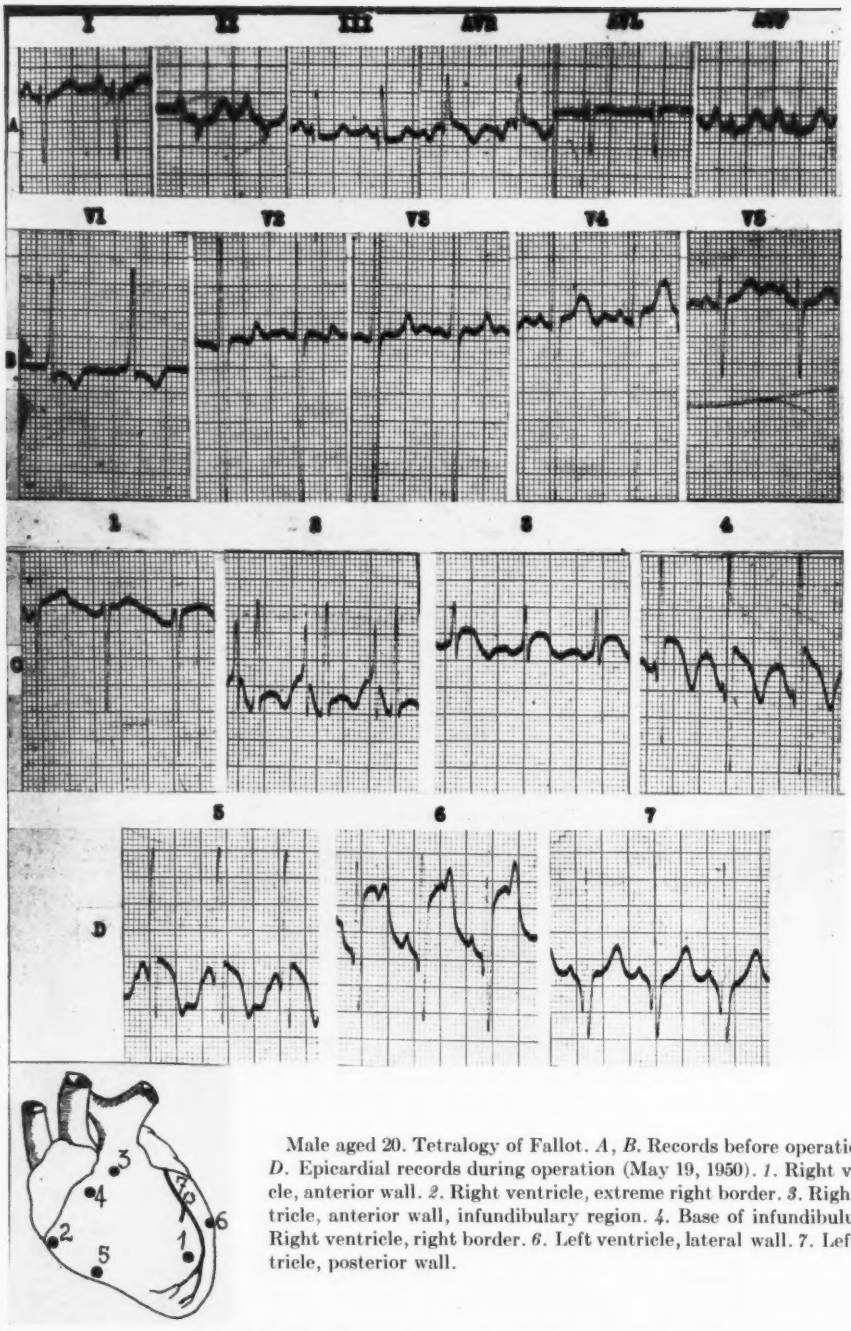
(*Text continued on page 56*)

FIG. 1. A comparison of the QRS pattern in conventional unipolar precordial leads with that in direct unipolar epicardial leads in a patient with tetralogy of Fallot, who had considerable right ventricular hypertrophy. The curves in *C* constitute the records obtained with the electrode in contact with the right auricular and right ventricular epicardium at the various indicated sites. The curves in *D* constitute the records obtained with the electrode in contact with the left ventricular epicardium at the various indicated sites over that chamber. The number over each tracing corresponds to the respective site, and so identifies the location of the exploring electrode. (The findings are explained in the text). Note in particular that a direct lead from high on the right auricle shows a QR pattern and that direct leads from the right ventricular epicardium are characterized by a large R wave, a late intrinsicoid deflection (0.09 second at point 3), and an absence of a Q wave. By contrast, the direct leads from the left ventricular epicardium are characterized by a large R wave preceded by a Q wave, a relatively unimpressive S wave, except when the electrode is in contact with the posterior wall of the left ventricle, and an intrinsicoid deflection that is not late (0.04 second at points 5, 7, and 8). The fact that a Q-S pattern preceded by a purely positive auricular deflection was recorded at point 6 suggests that this point was probably near the auriculoventricular junction.



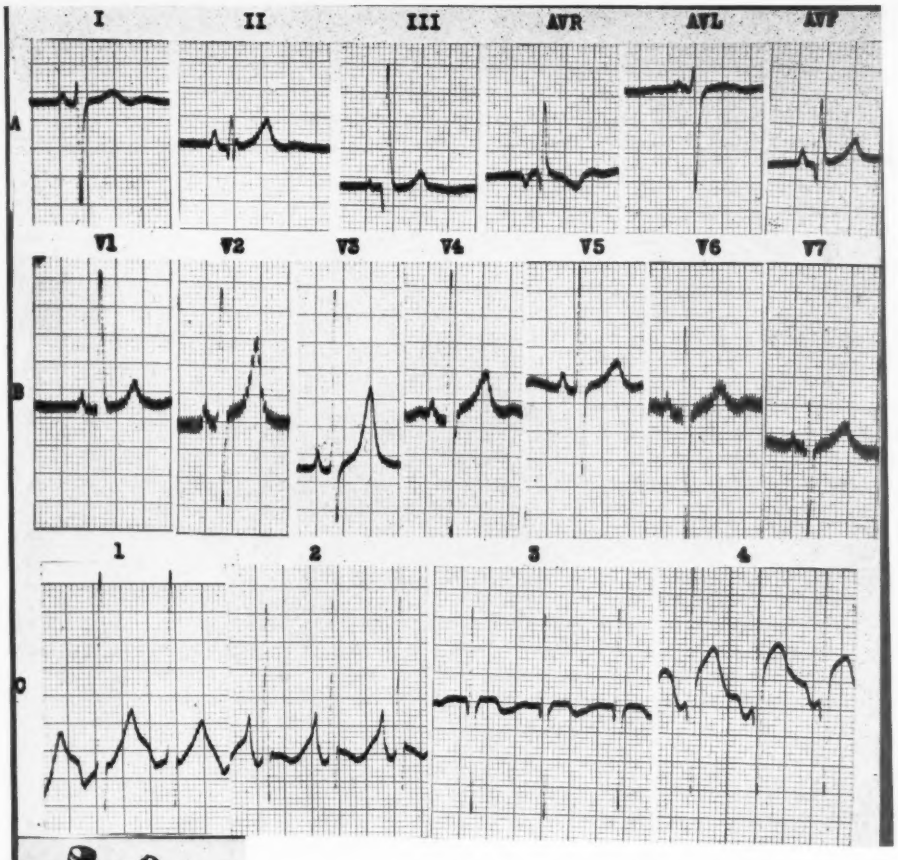
Female aged 20. Tetralogy of Fallot. *A*, *B*. Records before operation. *C*, *D*. Epicardial records during operation (June 17, 1950). *1*. Right auricle. *2*. Right ventricle, anterior wall. *3*. Right ventricle, anterior wall, close to right border. *4*. Right ventricle, right border. *5*. Left border of the heart, near the apex. *6*. Left ventricle, higher part of the posterior auriculoventricular groove. *7*. Left ventricle, posterior wall. *8*. Left ventricle, posterior wall.

FIGURE 1.



Male aged 20. Tetralogy of Fallot. *A*, *B*. Records before operation. *C*, *D*. Epicardial records during operation (May 19, 1950). *1*. Right ventricle, anterior wall. *2*. Right ventricle, extreme right border. *3*. Right ventricle, anterior wall, infundibulary region. *4*. Base of infundibulum. *5*. Right ventricle, right border. *6*. Left ventricle, lateral wall. 7. Left ventricle, posterior wall.

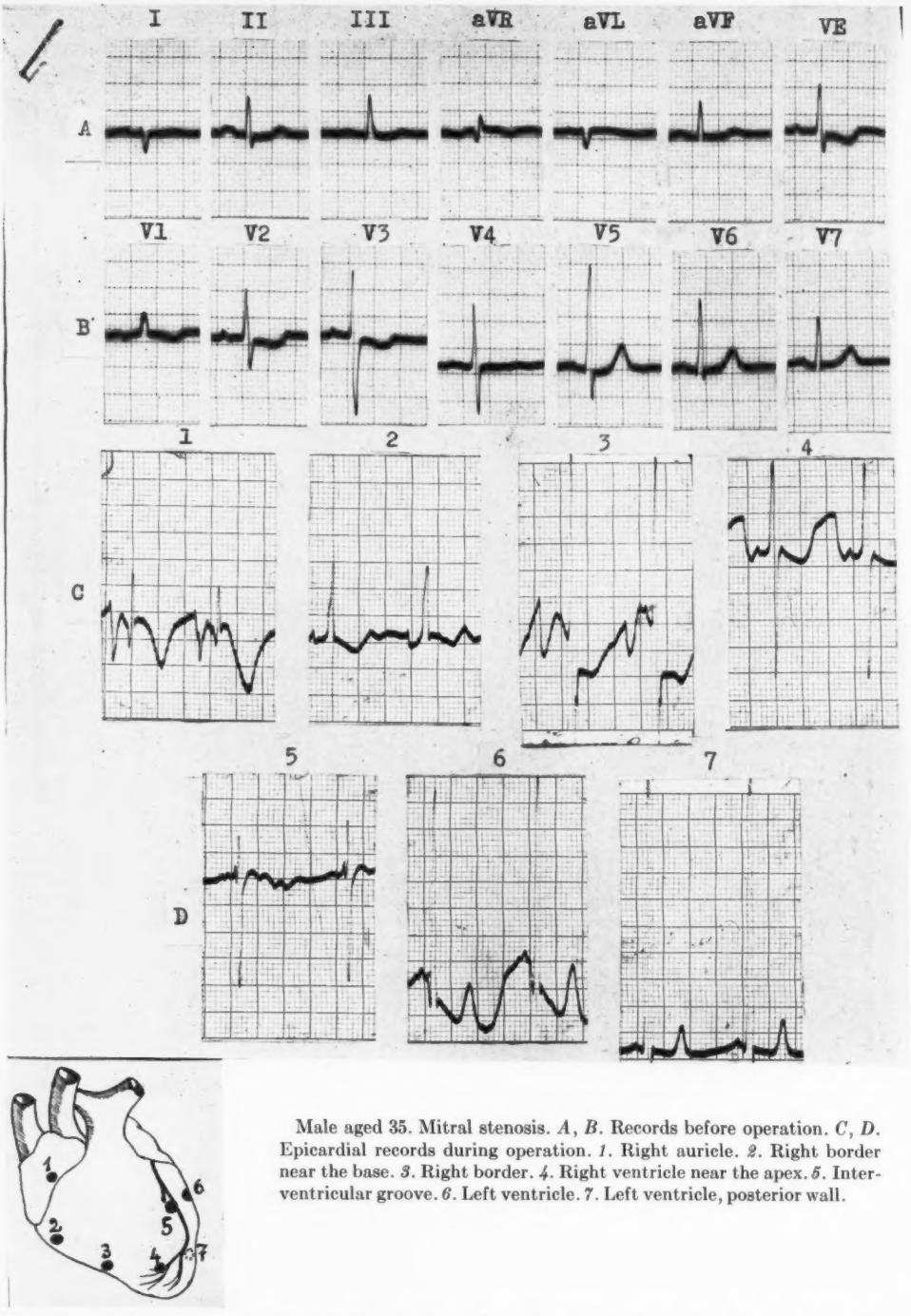
FIG. 2. A comparison of the QRS pattern in conventional unipolar precordial leads with that in direct unipolar epicardial leads in a patient with tetralogy of Fallot, who had considerable right ventricular hypertrophy. All curves in *C* and the first of *D* are the records obtained with the electrode in contact with the right ventricular epicardium at the various designated sites. The remaining curves in *D* are the records obtained with the electrode in contact with the left ventricular epicardium at the various designated sites over that chamber. The number over each trace corresponds to the respective site and thereby identifies the location of the exploring electrode employed in the deri-



Male aged 7. Tetralogy of Fallot. *A*, *B*. Records before operation. *C*. Epicardial records during operation (June 17, 1950). *1*. Right ventricle, right border. *2*. Right ventricle, higher part of the anterior wall. *3*. Left ventricle, higher part of the posterior wall. *4*. Left ventricle, lower part of the left border.

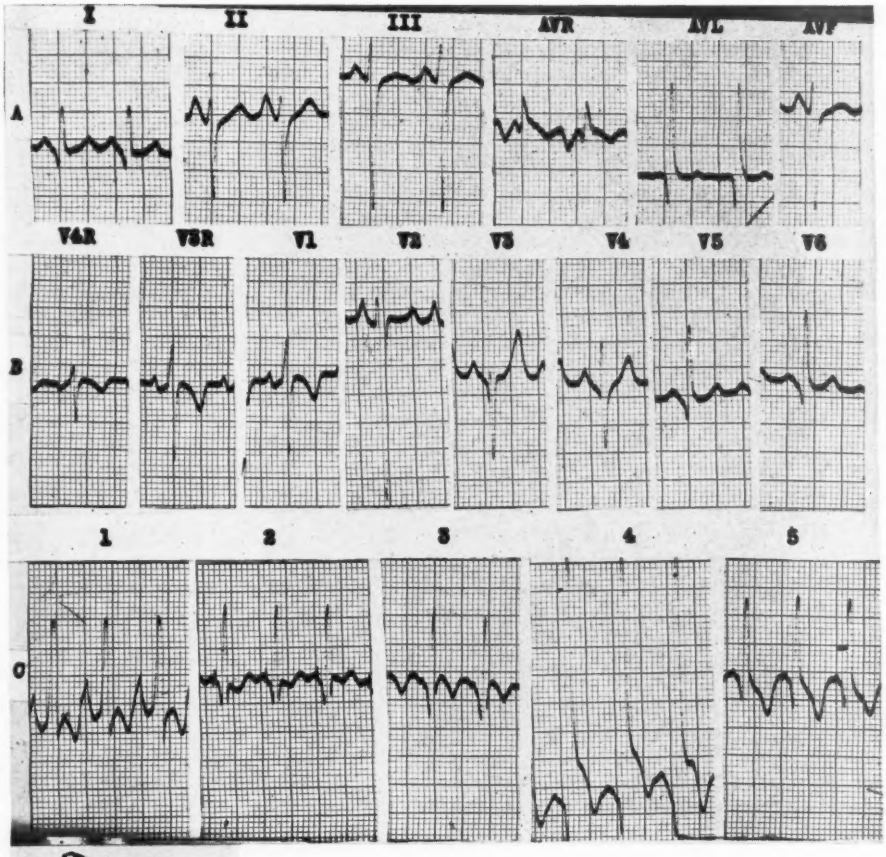
FIG. 3. A comparison of the QRS pattern in conventional unipolar precordial leads with that in direct unipolar epicardial leads in a patient with tetralogy of Fallot, with considerable right ventricular hypertrophy. The first two curves in *C* comprise the records obtained with the electrode in contact with the right ventricular epicardium at sites 1 and 2, and the last two curves in *C* are the records obtained with the electrode in contact with the left ventricular epicardium at sites 3 and 4. Note that direct leads from the designated sites of the right ventricular epicardium are characterized by a large R wave, a late intrinsicoid deflection (0.06 second), and an absence of a Q wave. By contrast, the direct leads from the left ventricular epicardium are characterized by a large R wave preceded by a Q wave, a relatively unimpressive S wave, and an intrinsicoid deflection that is not late (0.04 second).

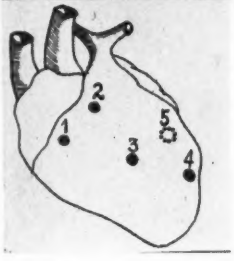
vation of the lead. (See text.) Except for a lead made with the electrode over the thinner trabecular zone (site 1), direct leads from the right ventricular epicardium are characterized by a large R wave, a late intrinsicoid deflection (0.07 second), and absence of a Q wave. By contrast, the direct leads from the left ventricular epicardium are characterized by a large R wave preceded by a Q wave, a relatively unimpressive S wave, and an intrinsicoid deflection that is not late (0.045 second). In several tracings from both the right and left ventricles, evidence of injury current is seen.



Male aged 35. Mitral stenosis. *A*, *B*. Records before operation. *C*, *D*. Epicardial records during operation. *1*. Right auricle. *2*. Right border near the base. *3*. Right border. *4*. Right ventricle near the apex. *5*. Interventricular groove. *6*. Left ventricle. *7*. Left ventricle, posterior wall.

FIG. 4. All the curves in *C* and the first in *D* constitute the records obtained with the electrode in contact with the right auricular and right ventricular epicardium at the various sites; the last two curves in *D* constitute tracings obtained with the electrode in contact with the left ventricular epicardium. Except for two leads, the first made with the electrode near the interventricular groove (site

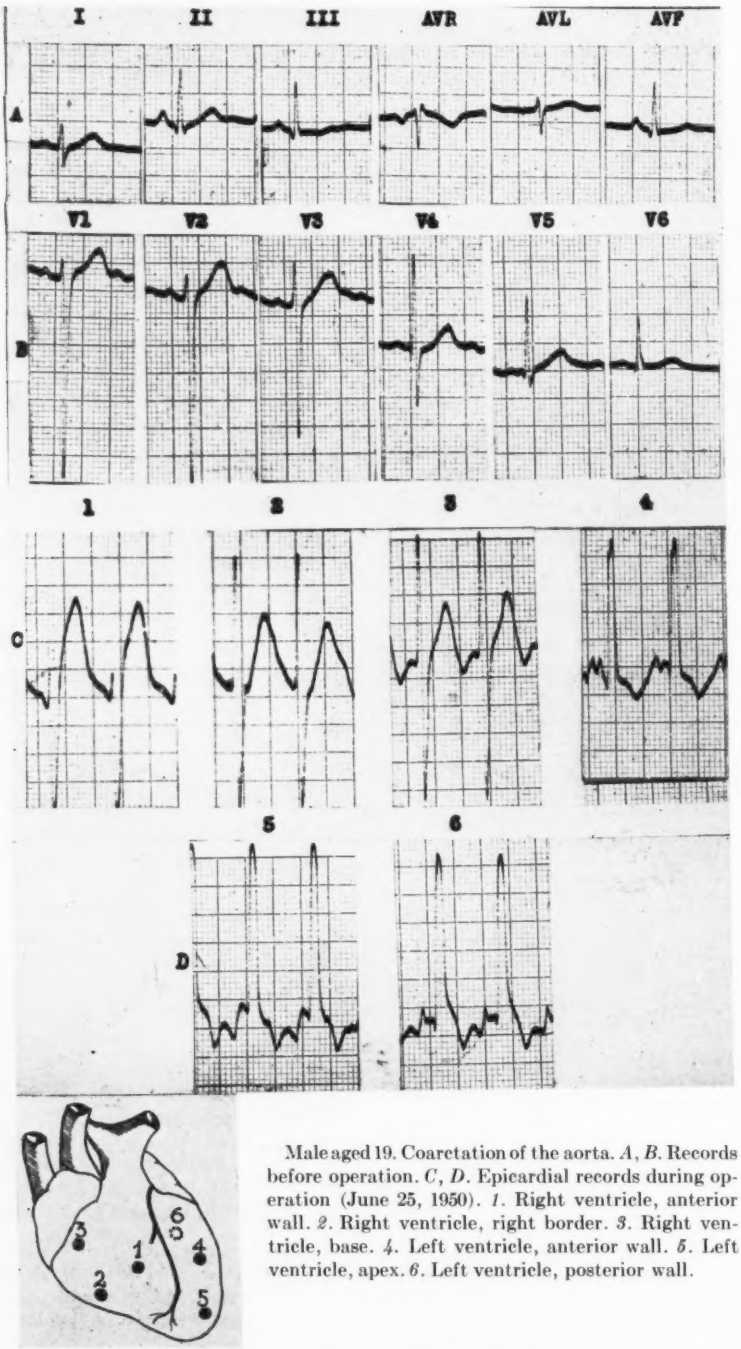




Male aged 10. Pulmonary atresia. *A*, *B*. Records before operation. *C*. Epicardial records during operation (June 3, 1950). *1*. Anterior wall of the heart near the right auricle. *2*. Anterior wall of the heart, higher part. *3*. Anterior wall of the heart, middle part. *4*. Left ventricle, near the left border. *5*. Left ventricle, posterior wall.

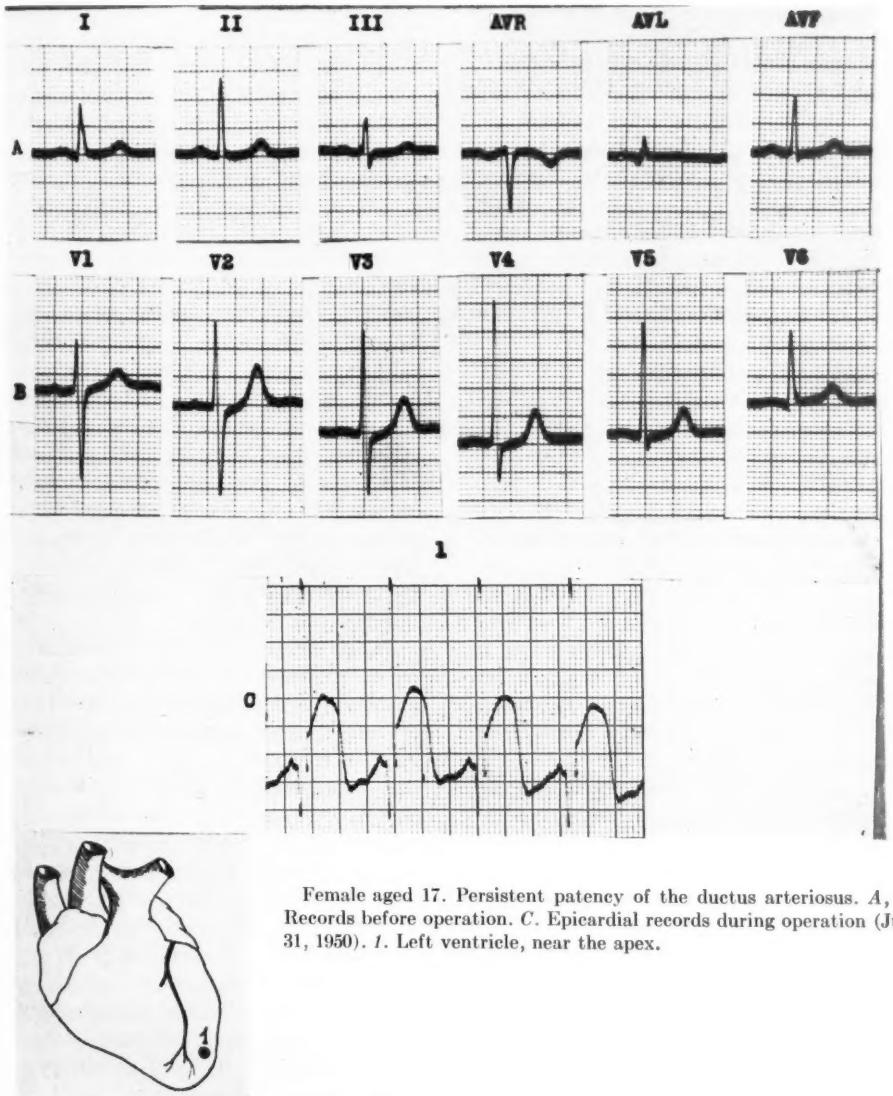
FIG. 5. A comparison of the QRS pattern in conventional unipolar precordial leads with that in direct unipolar epicardial leads in a patient with pulmonary atresia with considerable hypertrophy of the left ventricle. All the curves in *C* comprise the records obtained with the electrode in contact with the left ventricular epicardium at the five corresponding sites. In such direct leads, a large R wave preceded by a Q wave and a late intrinsicoid deflection (0.065 to 0.08 second) are the important findings.

5) and the other near the apex (site 4), direct leads from the right ventricular epicardium are characterized by a large R wave, late intrinsicoid deflection (0.06 second) and absence of a Q wave. By contrast, direct leads from the left ventricular epicardium are characterized by a very large R wave preceded by a Q wave, a small S wave and a slightly delayed intrinsicoid deflection. This slight delay can probably be attributed to a certain degree of left ventricular hypertrophy resulting from an associated mitral insufficiency. Note that the lead made with the electrode over the right auricle shows a qR pattern.



Male aged 19. Coarctation of the aorta. *A*, *B*. Records before operation. *C*, *D*. Epicardial records during operation (June 25, 1950). *1*. Right ventricle, anterior wall. *2*. Right ventricle, right border. *3*. Right ventricle, base. *4*. Left ventricle, anterior wall. *5*. Left ventricle, apex. *6*. Left ventricle, posterior wall.

FIG. 6. A comparison of the QRS pattern in conventional unipolar precordial leads with that in direct unipolar epicardial leads in a patient with coarctation of the aorta, who had definite hypertrophy of the left ventricle. The first three curves in *C* comprise the records obtained with the elec-



Female aged 17. Persistent patency of the ductus arteriosus. *A*, *B*. Records before operation. *C*. Epicardial records during operation (July 31, 1950). *1*. Left ventricle, near the apex.

FIG. 7. A comparison of the QRS pattern in conventional unipolar precordial leads with that in a single direct unipolar epicardial lead in a patient with persistent ductus arteriosus unassociated with any hypertrophy of either ventricle. The single curve in *C* is the record obtained with an electrode in contact with the left ventricle at the designated site near the cardiac apex. There is present a dominant R wave preceded by a prominent Q wave. This pattern corresponds essentially to the precordial lead from the left side zone.

trode in contact with the right ventricular epicardium at the corresponding sites. The last curve in *C* and the two curves in *D* are the records obtained with the electrode in contact with the left ventricular epicardium at the corresponding sites. In the direct leads derived from the right ventricular epicardium, a Q wave is lacking, the R wave is not the main deflection, and the intrinsicoid deflection is not late (0.04 to 0.045 second). By contrast, the direct leads from the left ventricular epicardium are characterized by a dominant R wave that is preceded by a Q wave and an intrinsicoid deflection that is late (0.09 second).

subject between the epicardial leads obtained at the time of operation and multiple unipolar precordial leads made in accordance with accepted methods, prior to the performance of the surgical procedure.

Results

The findings in the four cases exhibiting right ventricular hypertrophy are shown in figures 1, 2, 3 and 4. In summary they consist of (a) the presence of a delayed intrinsicoid deflection in epicardial leads derived from the right ventricle and an undelayed intrinsicoid deflection in epicardial leads derived from the left ventricle; (b) absence of a Q wave in epicardial leads derived from the right ventricle and the presence of a Q wave in epicardial leads of the left ventricle; (c) the presence of a dominant R wave in epicardial leads derived from the right as well as from the left ventricle; (d) the presence of an RS or rS type of QRS in epicardial leads derived from certain selected sites on the right ventricular surface; (e) the presence of an qR pattern in epicardial leads derived from the right auricle; (f) good correspondence between right-sided precordial leads and right ventricular epicardial leads; and (g) usual lack of correspondence between left-sided precordial leads and left ventricular epicardial leads.

The findings in the two cases exhibiting left ventricular hypertrophy are shown in figures 5 and 6. In summary, they consist of (a) the presence of a delayed intrinsicoid deflection in epicardial leads derived from the left ventricle and undelayed intrinsicoid deflection in epicardial leads derived from the right ventricle; (b) the absence of a Q wave in epicardial leads derived from the right ventricle and the presence of a Q wave in epicardial leads derived from the left ventricle; (c) the presence of a dominant R wave in epicardial leads derived from the left but not from the right ventricle; (d) good correspondence between right-sided precordial leads and right ventricular epicardial leads; and (e) good correspondence between left-sided precordial leads and left ventricular epicardial leads except that the intrinsicoid deflection in a left ventricular epicardial lead may be delayed even when it is undelayed in the left-sided precordial lead.

In the case of the patient with a persistent ductus arteriosus (fig. 7), unassociated with any ventricular hypertrophy, the QRS pattern in a single epicardial lead derived from a point on the left ventricle close to the cardiac apex is very similar to that in epicardial leads derived from the left ventricle in instances of left ventricular hypertrophy.

Discussion

To our knowledge, there have appeared up to now five papers concerned with direct exploration of the cardiac potentials of the human heart during operations which permitted exposure of the heart and the application of electrodes thereto.[1, 4–7] However, actual visceral epicardial leads were obtained in only two instances, one a case of purulent pericarditis[1] and the other a case of constrictive pericarditis.[5] So far as we are aware, the present study is the first to attempt a correlation between direct epicardial leads and unipolar precordial leads in instances of ventricular hypertrophy in man.

In our analysis of the data, we have purposely confined our observations to the form of QRS. Although it would have been desirable to study the pattern of the succeeding ventricular deflection as well, this proved to be impossible because of the modifications of the S-T segments in the direct leads which resulted from the injury currents induced by the physical contact of the exploring electrode with the visceral epicardium and by the alterations of repolarization influenced by variations in coronary flow and environmental temperature, which followed as a consequence of exposure of the heart to the atmosphere.

In the two cases of left ventricular hypertrophy, there was fairly good correspondence between the unipolar precordial leads from the right- and left-sided chest zones and the direct epicardial leads from the right and left ventricles, respectively. However, the same correlation was not strictly obtained in the cases exhibiting right ventricular hypertrophy. In these cases, precordial leads derived from the extreme left side of the chest were characterized by a deep S wave and absence of a Q wave, whereas the epicardial leads from the surface of the left ventricle were typical left ventricular epicardial leads, being characterized by a large

R wave which is preceded by a Q wave. To explain these differences between epicardial and precordial leads in cases exhibiting right ventricular hypertrophy, it can be assumed that during the phase of ventricular depolarization, the electrical field surrounding the heart is dominated by the electrical forces created during depolarization of the thickened right ventricle and that this dominant vector will be represented in contralateral precordial leads by oppositely directed deflections. With this interpretation, which is in accord with the conclusions of Barker and Valencia[2] and Goldberger,[3] the large R wave in a precordial lead from the right-sided zone and the deep S wave in a precordial lead from the left-sided zone are to be considered as electrocardiographic representations, in instances of right ventricular hypertrophy, of the same electrical force, that is, right ventricular potentials. An alternative explanation would be to consider the RS or rS pattern in left-sided precordial leads to be the result of a precordial electrode "facing" certain specialized zones of the right ventricular surface, epicardial leads from which are characterized by a QRS complex conforming to the RS or rS type.

Summary

1. For the first time, in man, direct epicardial leads have been obtained in four cases exhibiting right ventricular hypertrophy, in two cases exhibiting left ventricular hypertrophy and in one case without hypertrophy of either chamber.

2. In cases with right ventricular hypertrophy, the QRS complex in right ventricular epicardial leads is characterized by either an R, Rs, RS or rS pattern, depending on the portion of the right ventricular surface which is explored. In these same cases, the QRS complex in left ventricular epicardial leads is characterized by a qRs or qRS pattern.

3. In the cases with left ventricular hypertrophy, the QRS complex in right ventricular epicardial leads is characterized by an rs or RS pattern. In these same cases, the QRS complex in left ventricular epicardial leads is characterized by a qRs or qR pattern.

4. With one exception, there is good correspondence between right-sided precordial leads and right ventricular epicardial leads, as well as between left-sided precordial leads and left ventricular epicardial leads. The exception is the deep S wave in left-sided precordial leads in the cases of right ventricular hypertrophy. The rS or RS pattern in left-sided precordial leads, in such cases, is attributed to the spatial relationship between the exploring electrode and the portion of the right ventricular epicardium from which QRS is characterized by an rS and RS pattern.

Acknowledgments

We wish to express our deep gratitude to Dr. d'Allaines, head of the heart surgery center of the Broussais-La Charité Hospital in Paris, who has displayed personal interest in the objectives of this paper and who has offered us all the facilities to perform the studies.

We also wish to thank his assistants, Drs. C. Dubost, Allary and Lortat-Jacob for the valuable aid they have given us in making the electric recordings in the course of the surgical work.

We wish also to thank Dr. Donzelot for providing us with most of the clinical material forming the basis for this study.

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The Distribution of Body Fluids in Congestive Heart Failure

IV. Exchanges in Patients, Refractory to Mercurial Diuretics, Treated with Sodium and Potassium

By J. R. Elkinton, M.D., R. D. Squires, M.D., and L. W. Bluemle, Jr., M.D.

The clinical course was observed and balance studies were conducted in a series of patients with congestive heart failure who had hyponatremia and who had become refractory to mercurial diuretics. The data obtained during control periods and during treatment with hypertonic sodium solutions suggest that, in addition to sodium depletion, some disturbance is present in the mechanisms which regulate the water balance of the body. The administration of potassium did not appear to effect a diuresis.

In the previous paper[1] data were presented on the exchanges of water and electrolytes in patients with congestive heart failure during loss of their edema by diuresis. In the present communication similar studies are set forth of edematous patients who had become refractory to mercurial diuretics.

In the first paper of this series[2] the possible effects of certain changes in body fluid distribution on circulatory and renal function were discussed. Reduction of cardiac output, rate of glomerular filtration, and renal insufficiency are known to be regular effects of depletion of sodium ion,[3, 4] and the administration of sodium to salt-depleted subjects has been shown to restore the effectiveness of mercurial diuretics.[5, 6] Sodium depletion as a result of excessive administration of mercurial diuretics has been described by many observers[7–12] and has been termed by Schroeder "the low-salt syndrome." Since hyponatremia is a common finding in edematous cardiacs who have received mercurials,[13] it seemed pertinent to inquire whether loss of sodium in relation to water was the principal factor in the refractoriness of these patients to various diuretic measures.

Disturbances in the distribution of potassium have also been implicated in congestive heart failure. Newman and co-workers[14] and others,[15–17] as well as ourselves,[1] had shown that potassium may be retained in excess of nitrogen during the diuresis of the edema fluid. Fox and associates[18] have claimed that the administration of potassium to hyponatremic cardiacs, along with sodium, is a factor in the initiation of diuresis. For this reason the effect of potassium therapy in such patients requires study.

The purpose of this investigation was to determine in a group of hyponatremic mercurial-fast edematous cardiacs (1) whether the hyponatremia could be attributed to retention of water, to loss of sodium, or to both, (2) whether the raising of the extracellular concentration of sodium by the administration of hypertonic solutions of sodium would promote the onset of diuresis, and (3) whether the administration of potassium played a critical role in the diuresis of the edema fluid.

Experimental Methods and Procedure

Thirteen patients with peripheral edema due to heart disease were the subjects of study. All of these patients had become refractory to mercurial diuretics during sustained administration of the drug; most of them were hyponatremic. Nine of the patients were given hypertonic solutions of sodium during which time water was restricted; three were

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Laboratory facilities and personnel were aided by a grant from the National Heart Institute, United States Public Health Service, and by the C. Mahlon Kline Fund of the Department of Medicine.

During the study, J. R. E. was an Established Investigator of the American Heart Association.

given hypertonic sodium solutions and potassium; and two were given, on three occasions, potassium solutions only.

The clinical response in terms of sense of well-being, thirst, and diuresis were observed; the changes in components of the body fluids were calculated from data obtained by the balance technic. The details of procedure, the calculation of results, and the chemical methods were the same as those detailed in the previous paper.[1]

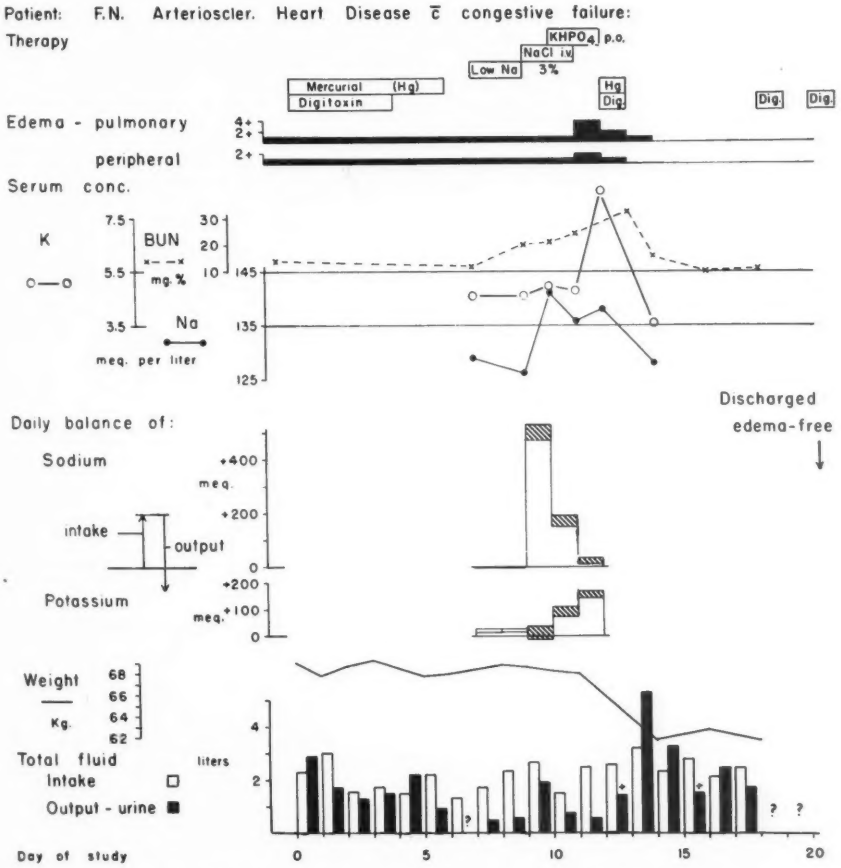

FIG. 1. Patient F. N.. Clinical course. Successful response to mercurial diuretic occurred following the administration of hypertonic sodium solution. This took place after recovery from acute left ventricular failure due to potassium cardiotoxicity induced by potassium therapy.

RESULTS

The results are presented in tables 1 to 3*B* and in figures 1 to 6.

Clinical Course. The diagnosis and clinical course of the 11 hyponatremic patients who were treated with hypertonic sodium solutions are tabulated in table 1 and illustrated in figures 1 to 6. All of the patients were still edematous despite intensive mercurial therapy immediately prior to the period of study. At least six of the 11 patients were hypotensive and eight were azotemic. All of the patients were weak and anorexic, one was cold and sweating, and four were mentally confused or comatose. One of these, R. S., who had the lowest serum level of sodium in the group, had a severe paralytic ileus simulating intestinal obstruction or mesenteric thrombosis. During treatment with hypertonic sodium solutions

TABLE 1.—*Patients with Congestive Heart Failure and Hyponatremia.*
Diagnosis and Clinical Course before, during, and after Hypertonic Sodium Therapy.

Patient	Age	Sex	Color	Diagnosis	Immediate prior Hg therapy		Azotemia	Hypotension	Signs and Symptoms		Restoration serum Na level	Diuresis		Hg therapy after Na therapy		Death after Na therapy
					doses	period			Before Na therapy	During Na therapy		During Na therapy	After Na therapy	doses	period	
						days									*days*	*days*
J. L.	58	M	W	Syphilitic, aortic insufficiency	7	10	+	±	Weakness, Cold sweating	Moderate thirst	Complete	None	Partial	1	4	14
H. W.	47	M	W	Arteriosel., Myocard. infarct.	5	16	+	+	Coma, Ileus	Thirst, Confusion	Complete	Moderate	Complete (before Hg)	1	8	44
J. F.	48	F	W	Chr. rheumatic, MI, MS, AI, AS	12	29	?	+	Weakness	Moderate thirst	Partial	None	Slight	1	3	4
R. S.	80	F	W	Hypertensive	6	17	+	+	Coma, Ileus	Moderate thirst	Partial	Slight	—	0		1
E. C.	38	M	W	Hypertensive	11	15	+	0	Weakness	Extreme thirst	Partial	None	None	4	7	?
H. B.	44	F	W	Chr. rheumatic, MS, Hodgkins dis.	20	20	+	+	Weakness, Confusion	Thirst	Partial	None	None	0		2
V. I.	63	M	W	Chr. rheumatic, SBE	13	26	+	?	Weakness	Thirst	Partial	None	None	0		3
E. L.	58	M	W	Chr. rheumatic, AS, AI, MS, MI	14	14	+	±	Confusion, Weakness		Partial	None	None	1	1	2
F. P.	24	M	W	Chr. rheumatic, MI, MS	6	11	0	+	Weakness		Slight	None	None	2	6	6
F. N.	68	M	N	Arteriosclerotic	6	6	+	+	Nausea, Weakness		Complete	Moderate	Complete	1	3	52
G. B.	39	F	N	Chr. rheumatic, MI, MS, AI, AS	5	11	0	0	Weakness		Complete	None	Slight	5	6	43

seven of the patients developed moderate to extreme thirst; in six of these this symptom appeared while the serum concentration of sodium was still below the range of normal values. Mainly because of this symptom, water restriction and sodium administration were carried to the point of complete restoration of the serum sodium to within the normal range in only four of the patients.

The therapeutic results of this treatment in terms of diuresis were inconstant. In only three of the patients was there a slight or moderate increase in urine flow during the period of administration of sodium, and in only five was there some degree of diuresis immediately after the sodium therapy (in four of these when mercurial diuretics were again instituted). In one, F. N., of the two patients who completely eliminated their edema, the diuresis appeared to be delayed by the deleterious effect of the potassium therapy (fig. 1). In the other of these two patients, H. W., the diuresis of water with very little salt continued after the administration of hypertonic sodium chloride (and before

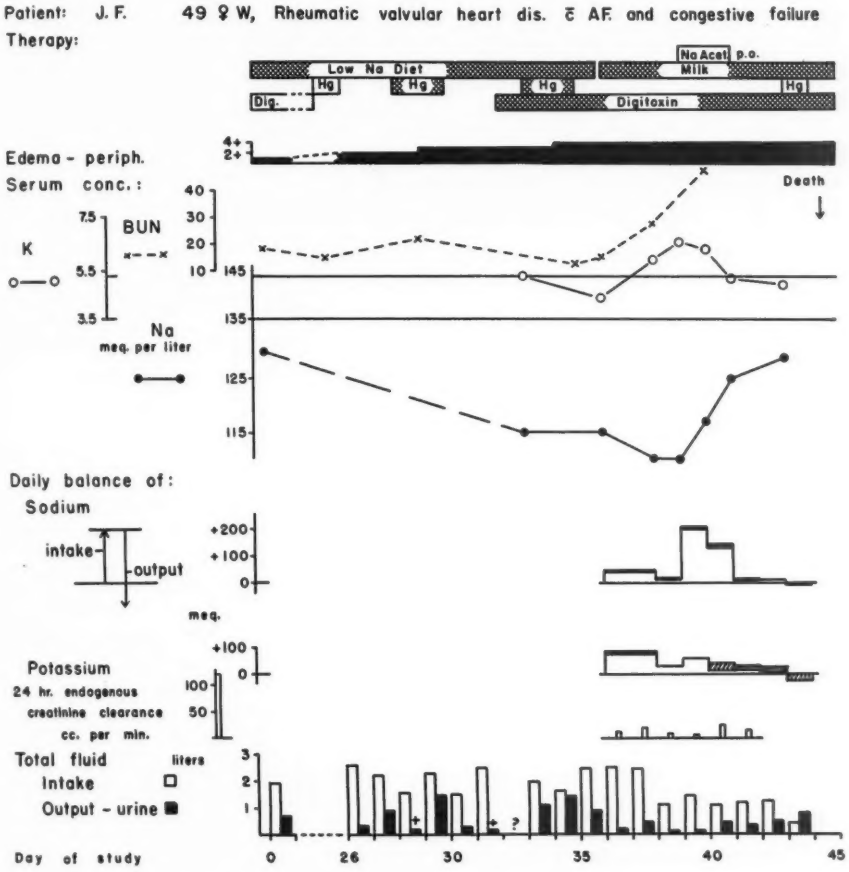

FIG. 2. Patient J. F. Clinical course. The serum sodium concentration continued to fall on days 37 and 38 despite a slightly positive sodium balance, indicating a primary retention of water. Following sodium therapy the serum concentration was partially restored but no diuresis occurred, even when mercury was given (day 44).

that of mercury) to the point where the edema was removed and the serum sodium concentration restored to high normal levels (fig. 3).

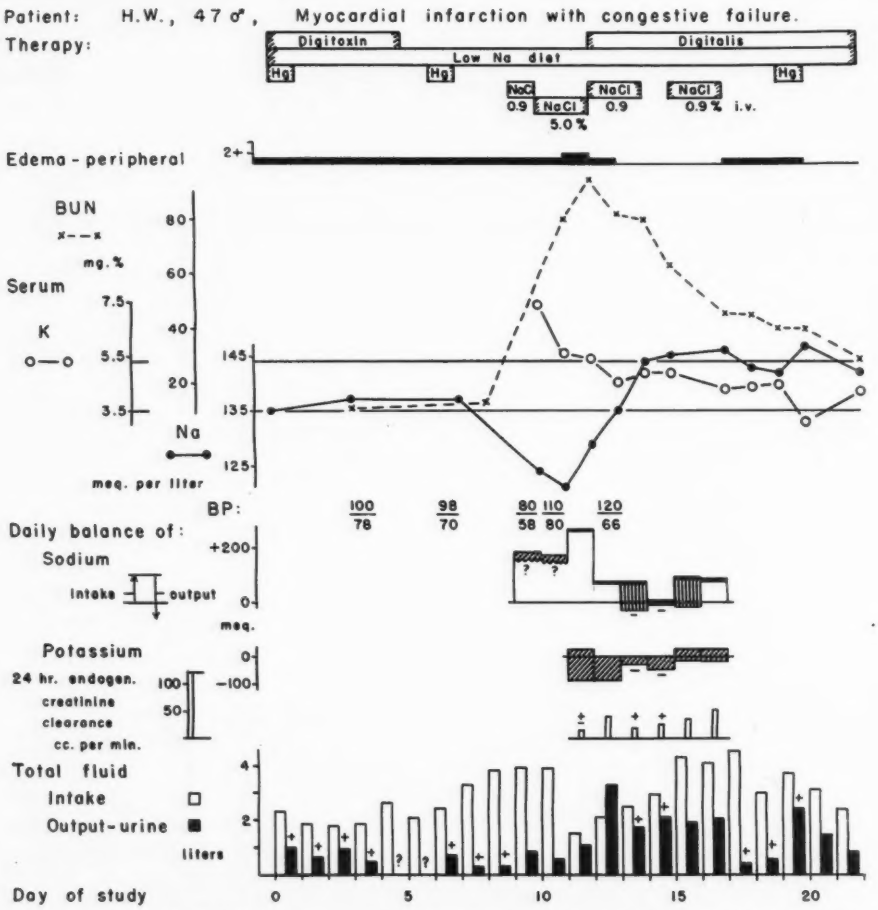

FIG. 3. Patient H. W. Clinical course. During the oliguric phase when the fluid intake was increased (days 8 to 11) the patient was hypotensive, the serum sodium level fell, and azotemia rapidly developed. On day 12 severe limitation of water intake plus hypertonic sodium therapy resulted in a rise in serum sodium concentration to 129 mEq. per liter and a moderate increase in urinary output. On days 13 to 15 when water intake was moderately restricted but no hypertonic salt was given, the patient excreted a large volume of water with very little salt, resulting in the loss of edema and a restoration of the serum sodium concentration to high normal levels. This readjustment occurred without the retention of potassium. Subsequently the blood urea nitrogen returned to normal levels.

The fact that death occurred within a week in six of the patients indicates, at most, that the sodium therapy as administered was not only ineffectual but may have been harmful, or at least, that the patient with chronic congestive failure who has become refractory to mercurials has an extremely poor prognosis under present therapy. In patient G. C., potassium was given alone or in conjunction with sodium during three different admissions (fig. 6), each time raising the serum level to abnormally high values. Only on the third admission can the potassium therapy possibly be interpreted to have accelerated the loss of edema. On the other admissions of this patient

no diuresis was associated with the administration of this ion. This was likewise true in the other two patients, G. B. and J. B., who retained large amounts of administered potassium (figs. 4 and 5*A*, tables 2*B* and 3*B*).

balance was zero or positive; that is, the concentration decrement was due to retention of water rather than to loss of sodium. When sodium ion was administered to the hyponatremic patients, the serum or extracellular con-

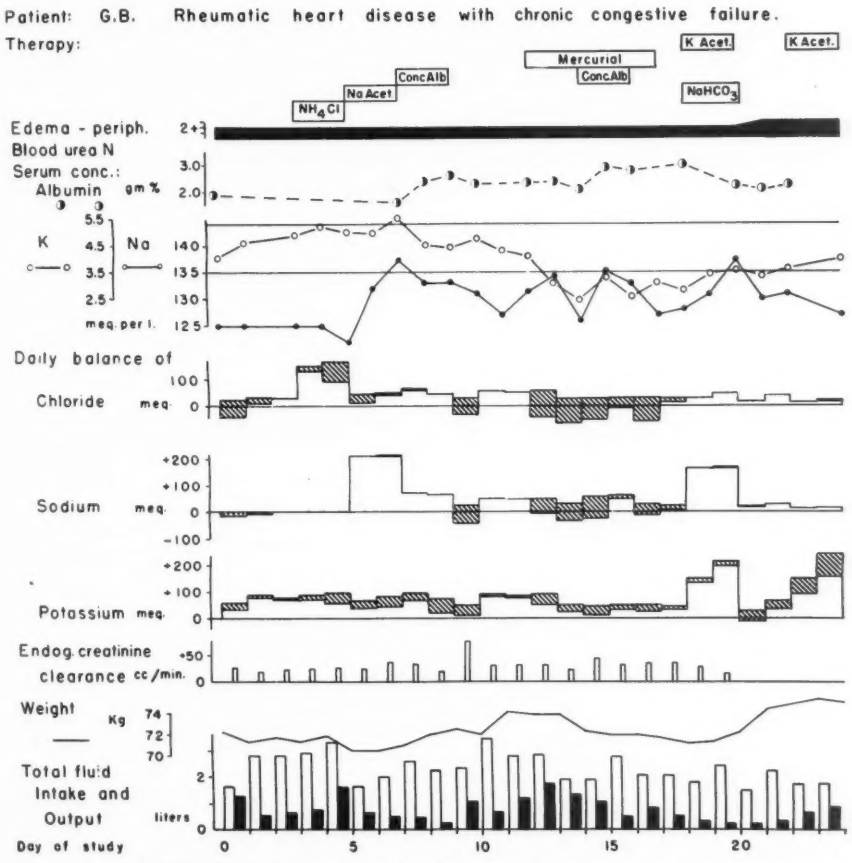

FIG. 4. Patient G. B. Clinical course. Despite the restoration of serum sodium concentration to normal levels on two occasions (days 6 to 7 and 18 to 20), the administration of concentrated albumin, and the administration of potassium, the patient failed to have a diuresis. The two relapses of the serum sodium concentration to hyponatremic levels without a negative sodium balance (days 8 to 11 and 20 to 24) suggest primary retention of water.

Sodium and Water Exchanges. In 12 of the 15 studies the initial serum sodium concentrations were abnormally low (table 3 and fig. 5). In six of seven periods in hyponatremic patients, when neither mercurials nor hypertonic sodium solutions were being given, the serum sodium concentration was observed to fall to still lower levels at a time when the sodium centration rose, and the chloride space expanded. However, in one patient, F. N., the total water of the body was demonstrated not to increase (table 3*B*), and in two other patients, H. W. and R. S., whose urinary output increased, the intake-output data suggest that during hypertonic sodium therapy their total body water was actually diminished (table 2*A*).

Following the sodium therapy two patients, F. N. and J. L., when given mercurials, excreted their edema fluid, presumably both water and salt (fig. 1). Patient H. W. likewise had a phase in a majority of the patients receiving hypertonic sodium therapy. But in three of the five patients in which changes in volume of the intracellular fluid was estimated, the fluid compartment was expanded rather than contracted (tables 2*B* and 3*B*), indicating that changes in intracellular as well as extracellular osmolarity were conditioning the distribution of water under these circumstances.

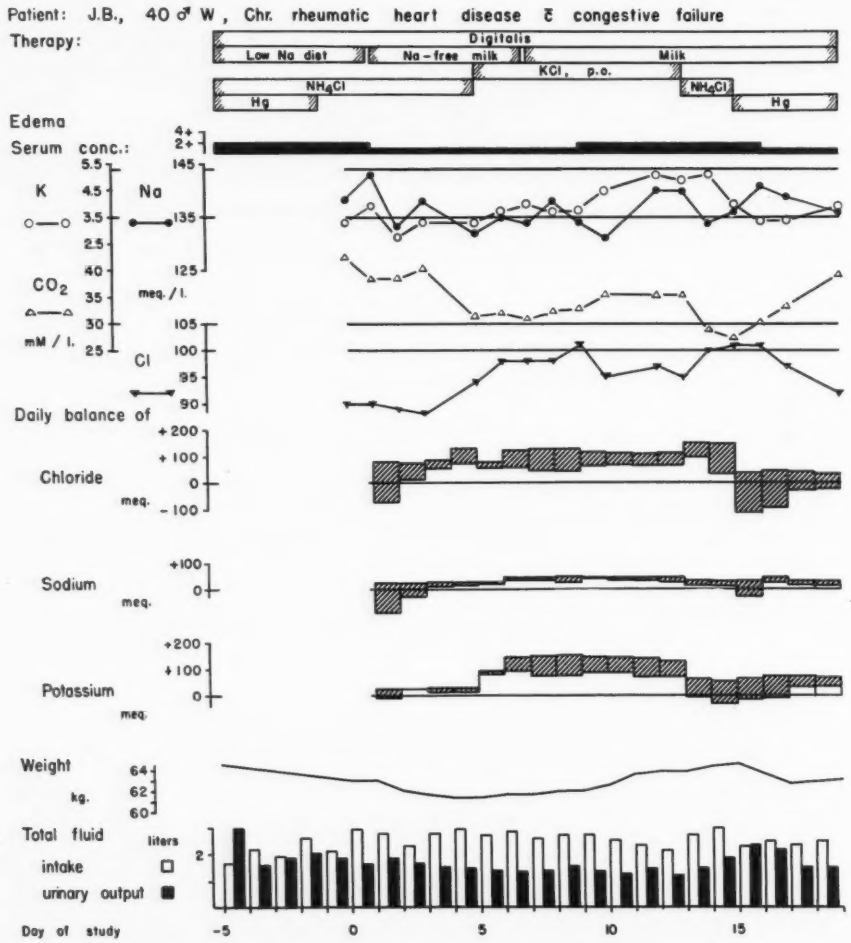

FIG. 5*A*. Patient J. B. Clinical course. The patient's metabolic alkalosis (elevated serum carbon dioxide) is shown to respond to the administration of ammonium chloride (days 1 to 5 and 14 to 15) and to be reinduced by mercurial diuretics (days 16 to 19). A rise in serum carbon dioxide was not prevented by the administration of potassium chloride nor was a diuresis initiated (days 6 to 13).

diuresis following hypertonic sodium therapy but excreted water greatly in excess of salt, further concentrating his total level of electrolyte (tables 2*A* and 2*B*, fig. 3).

Expansion of the extracellular phase must have been at the expense of the intracellular

Potassium Exchanges. The serum potassium

concentration was normal or elevated during the course of observation in 12 of the 15 studies; in only one patient, G. B., did the level fall to below 3.0 mEq. per liter (table 2*B*, fig. 3). Potassium was retained in the intracellular phase on all six occasions of its administration. In patients G. B. and J. B. the increase in intracellular potassium in excess of nitrogen amounted to 7.3 and 7.7 mEq. per Kg. of body weight, respectively, during the periods of potassium therapy (table 3*B*). In patient G. B. during the entire period of study of 21 days, during which time she was on a basic milk diet, the total retention of potassium in excess of nitrogen was 1015 mEq., or 13.5 mEq. per Kg. The calculated changes in intracellular sodium did not bear a reciprocal relation to those of intracellular potassium during many

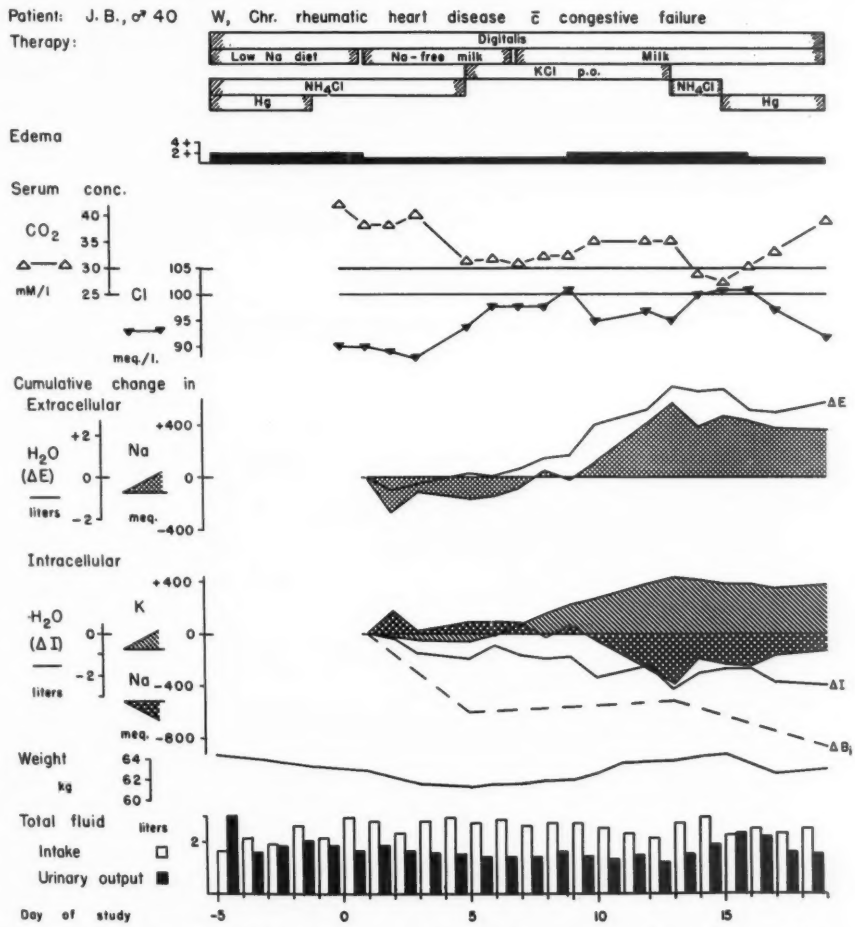

FIG. 5*B*. Patient J. B. Calculated changes in body fluid components. Intracellular sodium was not diminished and intracellular potassium was not increased when ammonium chloride was given and the serum carbon dioxide fell (days 1 to 5 and 14 to 15). Such exchanges did take place during potassium chloride therapy but the serum carbon dioxide content rose. Thus no recognized relationship appeared to occur between the extracellular alkalosis and exchanges of intracellular cations. Nor did any diuresis occur when potassium was retained in the cellular phase.

TABLE 2A.—*Patients Treated with Hypertonic Sodium Solutions. External Exchanges of Water, Electrolytes, and Nitrogen*

Patient	Period		Therapy	Average daily											Total period				
				Intake					Urinary output						IL*	Balance			
	Dates	Duration		H_2O	Cl	Na	K	N	Vol.	Cl	Na	K	N	Creatinine		Cl	Na	K	N
		days		*ml.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*ml.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mg.*	*Kg.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*
J. L.	9/28–10/3	5	House diet	Ad lib.	85±	85±	—	—											
	10/3–10	7	House diet + NaCl	1000	268±	268±	—	—											
	10/10–13	3	House diet + Hg†	1330	85±	85±	—	—											
H. W.‡	3/6–7	1	5% NaCl i.v.	1550	279	266	22	4.0	1090	4	3	107	7.6	781	—	+274	+261	− 85	− 3.6
	3/7–9	2	0.9% NaCl i.v.	2350	73	73	0	0	2535+	14+	6+	60+	21.2+	1208+	—	+ 46−	+ 36−	−120−	−42.8−
	3/9–12	3	0.9% NaCl i.v. + unlimit. H_2O	3805	60	59	18	3.1	2042+	9+	4+	42+	18.0+	849+	—	+ 94−	+ 88−	− 74−	−45.3−
J. F.	11/19–22	3	Milk	2033	38	35	66	—	257	10	2	5	—	133	—	+113	+ 96	+183	—
	11/22–24	2	Na acetate + milk	1280	37	177	51	6.2	308	4	5	16	2.9	184	—	+ 64	+339	+ 69	+ 6.5
	11/24–26	2	Milk	1200	21	16	29		463	1	1	17	—	—	—	+ 40	+ 27	+ 22	—
R. S.	11/9–10	1	2.9% NaCl i.v.	1750	839	839	0	0	1165	112	104	17	3.3	454	—	+726	+724	− 37	− 5.6
	11/10–11	1	4% NaCl i.v. + milk	1790	381	370	53	9.3	525	37	32	10	2.0	498	—	+335	+338	+ 43	+ 7.3
E. C.	6/15–17	2	2.5% NaCl i.v.	2135+	330	307	65	—	685	5	3	26	—	—	—	+648	+605	+ 78	—
H. B.§	5/4–5	1	Na-free milk	1000	26	1	52	5.3	265	7	1	9	1.9	122	1.9	−141	−193	+ 34	+ 1.3
	5/5–6	1	3% NaCl i.v.	1550+	261	253	41	5.0	60	2	1	1	0.2	11	—	+163	+135	+ 35	+ 3.3
V. I.	3/27–29	2	2% NaCl i.v.	1625	99	99	0	0	625	4	4	23	14.3	—	—	+358	+356	− 45	−14.3
	3/29–31	2	Na-free fluids	1088	2	2	0	0	585	3	2	21	8.4	426	—	− 4	− 3	− 41	−16.8
E. L.	12/28–29	1	3% NaCl i.v.	1420	261	260	9	0.9	790	9	3	39	6.7	—	—	+251	+255	− 30	− 5.8
	12/29–30	1	3.8% $NaHCO_3$ i.v.	2020	11	143	19	2.0	570	7	0	21	3.8	—	—	+ 3	+141	− 2	− 1.8
F.P.	10/14–17	3	Na-free milk	1750	38	1	76	—	565	2	0	38	—	—	3.3	+108	+ 2	+115	—
	10/17–18	1	Na-free milk	1900	13	0	39	—	390	1	0	42	—	263	1.2	+ 11	− 2	− 3	—
	10/18–19	1	3% NaCl i.v.	1740+	293	283	51	—	250	0	1	22	—		—	+232	+250	+ 21	—

* Insensible weight loss.

† Hg given on one day only.

‡ 650 and 500 ml. of pleural fluid withdrawn on 3/8–9 and 3/10–11, respectively, and included in total balances.

§ 1000 and 900 ml. of pleural fluid withdrawn on 5/4–5 and 5/5–6, respectively, and included in total balances.

of the periods of observation. During three of the five periods of potassium therapy and uptake by the cellular phase, when the final carbon dioxide content of serum was measured, a discrepancy between water shifts and cation transfers, was in the negative direction in most of the 19 periods of the six studies in which it could be calculated (tables 2*B* and 3*B*).

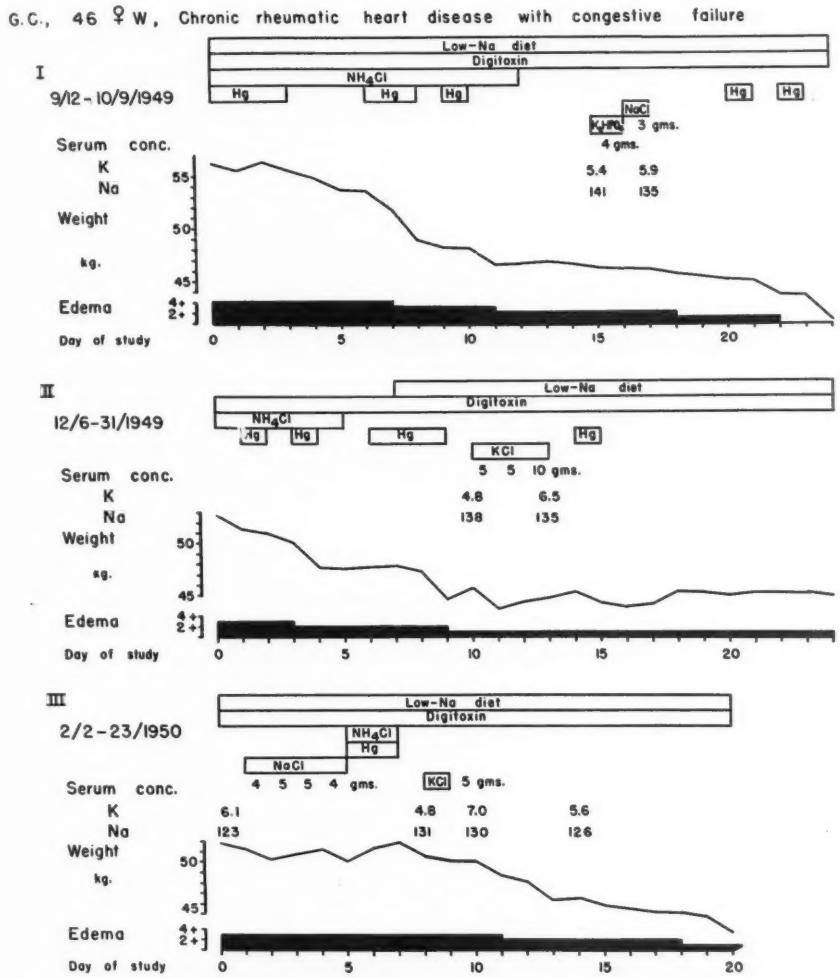

FIG. 6. Patient G. C. Clinical course. The temporal relationship of a few doses of potassium salts to the degree of edema and the changes in body weight are shown for three different admissions. On each admission potassium was retained in amounts sufficient to raise the serum concentration of the ion to supranormal levels. Only during admission III, and following sodium therapy for hyponatremia, did the administration of potassium coincide with an acceleration of the loss of weight and of edema fluid.

the serum bicarbonate concentration rose to abnormally high levels, rather than fell.

Osmotically Active Base. Change in osmotically active base, a calculated value indicating Changes in this value were in the positive direction in only six of the periods, in four of which hypertonic sodium solution was being given, and in one when potassium was ad-

TABLE 2B.—*Patients Treated with Hypertonic Solutions of Sodium*
Analyses of Blood and Serum, and Calculated Changes in the Body Fluids

Patient	Date	Period Duration	Therapy	Weight	Serum						Blood UN	Extracellular fluid volume*	Change in						
					Na	Cl	CO_2	K	H_2O‖	Creatinine			Total	Extracellular		Intracellular			Osmot. active base
													H_2O	H_2O	Na	H_2O	Na	K†	
		days		*Kg.*	*mEq. per L.*	*mEq. per L.*	*mM. per L.*	*mEq. per L.*	*Gm. per L.*	*mg. per cent*	*mg. per cent*	*liters*	*liters*	*liters*	*mEq.*	*liters*	*mEq.*	*mEq.*	*mEq.*
J. L.	9/28			69.6	126	88	28.8				44								
	10/3	5	House diet	69.6	121	86	25.2	5.4			47								
	10/10	7	NaCl + house diet	71.4	139			5.1			50								
	10/13	3	Hg + house diet	67.3	133	99	26.6	3.2			27								
H. W.	3/6			—	121	72	23.0	5.6	(940)	—	80	16.4							
	3/7	1	5% NaCl i.v.	—	129	84	25.6	5.4		—	94	17.0	—	+0.6	+225	—	+ 36	− 61	—
	3/9	2	0.9% NaCl i.v.	—	144	98	29.8	4.9		2.6	80	15.0	—	−2.0	− 35	—	+ 71	− 14	—
	3/12	3	0.9% NaCl + unlimit. H_2O	—	146	104	29.8	4.3		—	46	(15.0)	—	±0	+ 30	—	+ 56	+ 2	—
J. F.	11/19			—	115	91	23.4	4.5	935	—	15	(15.0)							
	11/22	3	Milk	—	110	86	—	6.6	(939)	0.7	—	17.1	—	+2.1	+155	—	− 40	+138‡	—
	11/24	2	Na acet. p.o.	—	125	85	31.0	5.4	939	0.9	48	18.0	—	+0.9	+370	—	− 31	+ 85	—
	11/26	2	Milk	—	129	87	—	5.0	(939)	—		18.0	—	±0	+ 90	—	− 63	+ 29	—
R. S.	11/9			—	104	58	30.6	3.5	(940)		39	(10.0)	—						
	11/10	1	2.9% NaCl i.v.	—	131	79	27.5	3.2			43	15.5	—	+5.5	+995	—	−271	− 39	—
E. C.	6/15			68.2	126	82	30.2	3.8	938		53	(17.0)							
	6/17	2	2.5% NaCl i.v.	69.3	133	90	28.4	4.1	(938)		47	21.9	+1.1§	+4.9	+785	−3.8	−180	+ 53‡	−188
H. B.	5/4			49.6	118	91	—	5.8	(940)		51	(12.0)							
	5/5	1	Na-free milk	46.8	119	97	21.6	5.1			56	10.0	−2.6	−2.0	−230	−0.6	+ 37	+ 50	−141
	5/6	1	3% NaCl i.v.	47.7	125	98	20.2	5.4			—	11.3	+1.1	+1.3	+225	+0.2	− 90	+ 17	+180
V. I.	3/27			—	114	79	30.6	6.1	(936)		74	(16.0)							
	3/29	2	2% NaCl i.v.	—	123	83	29.8	5.7	940		62	19.2	—	+3.2	+525	—	−169	11	—
	3/31	2	Na-free fluids	—	120	85	31.5	6.0	(945)		80	18.7	—	−0.5	−120	—	+117	− 3	—
E. L.	12/28			—	127	81	24.8	4.8	(930)		70	(15.0)							
	12/29	1	3% NaCl i.v.	—	135	87	26.0	5.5			84	16.5	—	+1.5	+330		75	35	—
	12/30	1	3.8% $NaHCO_3$ i.v.	—	128	86	26.0	4.9			116	16.7	—	+0.2	− 90	—	+231	+ 11	—
F. P.	10/14			54.7	126	84	35.1	—	945		13	(15.0)							

	12/30	1	3.8% $NaHCO_3$ i.v.	—	128	86	26.0	4.9		116	16.7	—	+0.2	− 90	—	+231	+ 11	—	
F. P.	10/14			54.7	126	84	35.1	—	945		13	(15.0)							
	10/17	3	Na-free milk	55.0	120	87	27.0	6.7	(945)		17	15.6	+0.3§	+0.6	− 15	−0.3	+ 17		317
	10/18	1	Na-free milk	55.3	123	80	—	—	945		24	17.2	+0.3§	+1.6	+240	−1.3	−242	—	+165
	10/19	1	3% NaCl	56.8	120	90	28.4	6.4	(945)		28	17.6	+1.5§	+0.4	± 0	+1.1	+250	—	−181

* Calculated by changes in chloride balance forward or backward from assumed volume in parentheses.

† In excess of nitrogen except where noted.

‡ Total ΔK_I, not just in excess of nitrogen.

§ Assumed to equal change in weight.

‖ Calculated from serum total protein concentration except where value was assumed (parentheses).

In this table and in table 3*B* time as designated by date indicates end of period at which time serum analyses were made, balances for the period determined, and exchanges calculated.

TABLE 3*A*.—*Patients Treated with Sodium plus Potassium or Potassium Alone. External Exchanges of Water, Electrolytes, and Nitrogen*

Patient†	Period		Therapy	Average daily										Total period				
				Oral intake					Urinary output						IL*	Balance			
	Dates	Duration		H_2O	Cl	Na	K	N	Vol.	Cl	Na	K	N	Creatinine		Cl	Na	K	N
		days		*ml.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*ml.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mg.*	*Kg.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*
F. N.	5/31–6/2	2	Na-free milk	2000	16	1	25	3.2	500	15	5	14	3.4		2.6	+ 1	− 10	+ 23	− 0.4
	6/2–3	1	3% NaCl i.v. + milk	2620	536	530	39	4.1	1905	130	54	52	9.2		1.2	+405	+474	− 13	− 5.1
	6/3–4	1	2% NaCl i.v. + K_2HPO_4 p.o.	1500	201	193	114	5.0	745	73	42	37	3.5		0.9	+127	+149	+ 77	+ 1.5
	6/4–5	1	K_2HPO_4 p.o. + milk	2500	45	33	171	7.5	585	59	31	30	3.2		—	− 15	± 0	+141	+ 4.3
G. B.	11/4–9	5	Na-free milk + NH_4Cl p.o.	2688	80	2	83	7.4	986	32	4	20	6.9	349	9.7	+210	− 24	+308	+ 2.3
	11/9–11	2	Na acetate p.o. + milk	1830	46	215	75	8.0	583	19	3	35	7.1	437	2.0	+ 52	+417	+ 81	+ 1.8
	11/11–16	5	Conc. alb. i.v. + milk	2648	51	54	81	15.1	746	14	14	33	6.6	497	6.7	+181	+193	+250	+42.6
	11/16–22	6	Hg + conc. alb. + milk	2278	35	43	56	13.8	1027	61	34	27	6.7	418	10.0	−217	− 20	+170	+42.7
	11/22–24	2	$NaHCO_3$ i.v. + K acet. p.o.	2188	37	167	185	9.2	285	0	4	18	4.0	274	2.3	+ 72	+322	+334	+10.4
	11/24–28	4	K acetate p.o.	1828	21	18	121	5.2	518	0	3	35	4.7	—	2.9	+ 77	+ 54	+280	+ 2.3
J. B.	2/9–13	4	Na-free milk + NH_4Cl	2731	94	25	27	18.8	1655	72	44	23	9.0		6.1	+ 84	− 82	+ 16	+39.2
	2/13–21	8	Milk + KCl	2604	106	42	129	14.9	1368	56	8	59	9.4		7.3	+451	+263	+642	+44.0
	2/21–23	2	Milk + NH_4Cl	2885	148	35	59	12.4	1585	80	14	79	9.0		1.9	+134	+ 30	− 39	+ 6.8
	2/23–27	4	Milk + Hg	2425	41	37	69	13.7	1888	103	29	60	8.8		3.8	−253	+ 25	+ 35	+19.4

* Insensible weight loss.

† Data obtained during the three studies on patient G. C. are presented graphically only, in figure 6.

TABLE 3*B*.—*Patients Treated with Sodium Plus Potassium or with Potassium Alone. Analyses of Blood and Serum, and Calculated Changes in the Body Fluids*

Patient	Date	Period duration	Therapy	Weight	Serum						Blood	Extracellular fluid volume*	Change in						
					Na	Cl	CO_2	K	H_2O‖	Creatinine	UN		Total	Extracellular		Intracellular			Osmot. active base
													H_2O	H_2O	Na	H_2O	Na	K†	
		days		*Kg.*	*mEq. per L.*	*mEq. per L.*	*mM. per L.*	*mEq. per L.*	*Gm. per L.*	*mg. per 100 cc.*	*mg. pe 100 cc.*	*liters*	*liters*	*liters*	*mEq.*	*liters*	*mEq.*	*mEq.*	*mEq*
F. N.	5–31			68.4	129	88	25.0	4.6	(934)		12	(17.0)							
	6–2	2	Na-free milk	68.7	126	86	25.0	4.6	934		20	17.4	+0.9	+0.4	± 0	+0.5	+ 10	+ 31	− 33
	6–3	1	3% NaCl i.v.	68.2	141	94	23.9	4.9	(934)		21	19.7	−0.3	+2.3	+390	−2.6	+ 84	− 11	+219
	6–4	1	2% NaCl + K_2HPO_4	68.0	136	98	20.7	4.8	(934)		24	20.0	−0.1	+0.3	− 55	−0.4	+204	+ 71	−476
	6–5	1	K_2HPO_4 p.o.	—	138	95	—	8.0	(934)		—	20.6	—	+0.6	+120	—	−120	+ 66	—
G. B.	11–4			72.2	125	92	24.3	4.0	941	1.1	18	(15.2)							
	11–9	5	NH_4Cl p.o.	70.5	122	94	24.8	5.0	(942)	—	16	16.9	+0.2	+1.7	+165	−1.5	−189	+299	−414
	11–11	2	Na acet. p.o.	71.0	137	95	33.4	5.5	943	1.0	14	17.2	+0.7	+0.3	+295	+0.4	+122	+ 67	+362
	11–16	5	Conc. alb. i.v. + H_2O p.o.	73.9	131	92	27.9	4.1	940	0.9	13	19.5	+2.7	+2.3	+210	+0.4	− 59	+163	−363
	11–22	6	Hg + conc. alb.	71.2	128	88	30.2	2.8	939	0.9	18	18.1	−2.6	−1.4	−225	−1.2	+195	+ 97	−552
	11–24	2	$NaHCO_3$ i.v. + K acet. p.o.	72.7	137	87	40.1	3.5	939	0.8	—	19.0	+1.5	+0.9	+290	+0.6	+ 32	+293	+ 34
	11–28	4	K acet. p.o.	75.0	127	83	—	4.0	940	—	—	20.9	+2.3	+1.9	+ 40	+0.4	+ 14	+257	−606
J. B.	2–9			63.0	143	90	38.6	3.9	(940)			(16.0)							
	2–13	4	Na-free milk + NH_4Cl	61.3	132	94	31.5	3.3				16.2	−1.0	+0.2	−165	−1.2	+ 83	− 69	−604
	2–21	8	Milk + KCl	63.8	140	95	35.5	4.9				20.3	+2.7	+4.1	+730	−1.4	−467	+491	+ 95
	2–23	2	Milk + NH_4Cl	64.5	136	101	27.4	4.0				20.2	+0.8	−0.1	−115	+0.9	+145	− 36	−111
	2–27	4	Milk + Hg	63.0	136	92	39.2	3.9				19.6	−1.3	−0.6	− 85	−0.7	+110	− 5	−250

*, †, ‖ as in Table 2*B*.

ministered. These positive values were not associated with diuresis. Total change in osmotically active base for each of six studies amounted to 28 to 125 per cent of the total external transfers of sodium plus potassium.

Discussion

The observations in these patients have not been complete enough to yield definitive data on the problems outlined in the introduction. Obviously, the lack of measurements of general and renal hemodynamics and of regional differences in fluid distribution prevents accurate assessment of the effect of changes in the systemic circulation on the loss of edema. Nevertheless, these studies do permit a few conclusions to be drawn in respect to this type of patient, and the findings demonstrate that the problem is not a simple one.

The response of some of the patients to hypertonic solutions of sodium indicates that sodium depletion is sometimes a factor in the oliguria of hyponatremic cardiac patients. The presence of hypotension and the symptoms of weakness and occasional ileus support this interpretation. Sodium depletion is not ruled out by the failure of a majority of these patients to have a diuresis following such therapy in their particular instance; other factors must be involved as well. The facts that the serum sodium concentration continues to fall when the sodium is not being lost, that during sodium administration thirst appears long before the serum sodium reaches normal, and that after therapy the serum sodium concentration frequently returns to its previous low level, strongly suggest that some process is operative in these patients which requires the maintenance of a lower than normal total concentration of electrolytes. In the previous study[1] it was shown that during diuresis of edema fluid intracellular water was lost, and that intracellular base was being inactivated. As was pointed out in the discussion of this problem in the first paper[2] such a process might result in intracellular dehydration in the presence of a low concentration of electrolyte (or hyponatremia), an intracellular abnormality that might through humoral mechanisms inhibit the excretion of water and salt. Since no measurements were made either of the absolute volume of the intracellular fluid compartment, or of antidiuretic hormone production, these particular studies neither confirm nor deny this hypothesis.

The hyponatremia that occurs in other states of sodium depletion, such as in gastrointestinal fluid loss, sweating, or adrenocortical insufficiency, usually appears after the initial stages of the conditions. Where the fluid lost is isotonic (as in succus entericus) or hypotonic (as in sweat) the onset of hyponatremia is dependent upon the acquisition of salt-free water. Peters[19] has interpreted the fall in total electrolyte concentration to indicate that under such stress the volume of body fluids is more zealously guarded than composition. While such an interpretation is possible in these cases, not only is the mechanism of such a teleologic homeostasis quite unknown, but the recurrence of hyponatremia following sodium therapy is strongly against such an interpretation. It seems reasonable, therefore, to seek some explanation such as intrinsic change in intracellular osmolarity.

The role that mercury has played in these cases is somewhat obscure. It is entirely possible that the development of resistance to the diuretic action of mercurial preparations was quite unrelated to the drug and was due to other factors of central, peripheral, and renal circulatory failure. On the other hand, the occurrence of hyponatremia seemed to be more common in cardiac patients who had received mercury than in those who had not,[13] and the patients reported in this paper had certainly had intense mercury therapy (table 1). Mercury appears to be a poison to certain cytologic enzyme systems, including those responsible for electrolyte transport in the cells of the renal tubule.[20] It is not inconceivable that it may effect intracellular processes in other tissues as well.

Potassium therapy was hardly given a fair trial; it was tried in too few cases in large enough amounts. When it was given, it was retained in cells in excess of nitrogen. Retention of this fraction of the ion in amounts of 7.3 and 7.7 mEq. per Kg. of body weight is comparable to the retention in other types of postassium deficiency.[21] But even in patient G. B., in whom the total retention of 13.5

mEq. per Kg. was equivalent to that of severe cases of infant diarrhea,[22] diabetic acidosis,[23] or metabolic alkalosis due to starvation or ACTH therapy,[24] the retention of potassium produced no diuresis.

The metabolic alkalosis which was present in these patients did not appear to be related to abnormalities of potassium or sodium content of the intracellular phase, as reported in other conditions.[24, 25] In patient J. B. the extracellular bicarbonate concentration fell when ammonium chloride was given and rose when mercury was given, without significant change in cellular sodium or potassium (fig. 5). This fits in with the evidence in the previous studies[13] that the metabolic alkalosis found in some of these edematous cardiac patients is caused by the relatively high rate of excretion of chloride in respect to sodium during diuresis, rather than to a response to primary carbonic acid retention or to intracellular cation abnormalities.

Schwartz and Wallace have reported[17] that when sodium moved into the intracellular phase during mercurial diuresis the patients became refractory to the drug. When ammonium chloride was administered, the sodium left the cells as potassium was taken up, and the patients again responded to mercury. Exchanges of intracellular sodium did not appear to play such a critical role in the cases reported here. In patient G. B. the administration of ammonium chloride led to some loss of cellular sodium but no diuresis (although mercury was not given immediately) (table 2*B*). In patient J. B. the administration of potassium resulted in loss of intracellular sodium but did not prevent a rise in serum bicarbonate concentration, nor did it lead to a diuresis immediately or subsequently when ammonium chloride and mercurials were given (fig. 5*B*). Miller[16] has stated that sodium as well as potassium regularly enters cells during diuresis and interprets this to mean that these ions leave this phase during the development of edema. He suggests that primary water retention has occurred with movement of sodium from cells to the diluted extracellular fluid. Our studies confirm the development of intracellular potassium deficiency, but we interpret our data to indicate that changes in osmolarity of solutes within the cell are quantitatively more important than transfers of sodium across the cell boundary.

The practical therapeutics of the hyponatremic cardiac patient refractory to mercurial diuretics remain to be clarified. Certainly some of these patients need sodium ion in hypertonic solution. Such patients are those with severe hyponatremia, with azotemia, and with evidence of peripheral vascular collapse: weakness, cold sweating, and hypotension. When these findings are present the authors believe that such therapy should be tried. It is impossible, however, at the present time, to predict whether such therapy will be successful. We do not know enough concerning the other factors involved. The factor of time, or speed of therapy, is probably very important. Patient R. S. may well have been lost because the sodium was administered too rapidly. Patient H. W. was given hypertonic sodium solution with much greater restraint (less sodium over a longer period of time); the immediate effect on his renal function was much better than in patient R. S. Perhaps rehydration of cells which must result from Schemm's treatment[26] plays an important part in the initiation of diuresis. A great deal more observation is needed to work out the precise therapeutic indications of this syndrome.

Summary and Conclusions

Fifteen balance studies were carried out in 13 edematous cardiac patients, most of whom were hyponatremic, and all of whom had become refractory to mercurial diuretics. The majority were given hypertonic sodium solution, some received potassium, and a few were given both ions.

During control periods in six patients the serum sodium concentration fell to even lower levels when the patient was in sodium equilibrium or was retaining sodium.

The administration of hypertonic sodium solution resulted in some degree of diuresis in only five of 11 patients; in only two was the edema completely eliminated. Most of the patients developed thirst while still hyponatremic.

The administration of potassium, with or without sodium, to a few of the patients was

not associated with any diuresis, although potassium was retained in the cellular phase.

It is concluded that while systemic sodium depletion may be present, may be depressing the circulation, and may be treated successfully with hypertonic sodium solution, other factors are involved in this syndrome leading to retention of water rather than to loss of salt. Alteration in intracellular osmolarity may be one of these. Only when these factors are understood will the precise indications for therapy of this syndrome be known.

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The Size of the Heart during the Course of Essential Hypertension

By MORRIS KLEINFELD, M.D., AND JULES REDISH, M.D.

Changes in cardiac size, as measured by teleroentgenogram, in the course of essential hypertension were studied in 45 patients. Although the majority showed progressive cardiac enlargement from the discovery of hypertension, a goodly number revealed a stationary cardiac size for 10 or more years. Congestive heart failure was found to occur with normal heart measurements. Weight loss did not affect a reduction in cardiac size. Normal cardiac measurements for a decade or more were not unusual. Marked cardiac enlargement was present in several patients for 10 years with little functional limitation. Prognosis on the basis of cardiac size alone was unwarranted.

THIS study is primarily concerned with the changes in the size of the heart occurring in the course of essential hypertension. Factors such as congestive heart failure, myocardial infarction, degree and duration of hypertension and loss of body weight are evaluated in relation to the size of the heart.

MATERIAL AND METHOD

Patients were chosen from the files of the Adult Cardiac Clinic, Third (New York University) Medical Division of Bellevue Hospital. All had essential hypertension, that is, persistent elevation of the diastolic pressure above 90 mm. Hg with no demonstrable cause. No other cause for heart disease was present except arteriosclerosis, which was considered a complicating factor. All patients were observed for five years or more and all had an adequate number of teleroentgenograms taken over this same period. A total of 45 patients fulfilled these criteria.

This group of 45 patients was arbitrarily divided into three categories depending upon the level of the blood pressure. Those patients with diastolic readings persistently between 90 mm. Hg and 120 mm. Hg were called "moderate" and those with diastolic readings higher than 120 mm. Hg were considered "marked" hypertensives. Those patients who displayed levels that varied considerably in the hypertensive range, as defined, were called "labile."

For the sake of simplicity, cardiac mensuration was confined to determination of the maximum transverse diameter of the cardiac silhouette in the posteroanterior projection. The per cent deviation from the normal was obtained by comparing the maximum transverse diameter with the predicted diameter as obtained from the tables of Ungerleider and Clark.[1] Deviations of more than 10 per cent were considered abnormal; hearts with transverse diameters between 11 and 15 per cent above predicted values were called "moderately enlarged," those above 15 per cent were considered "markedly enlarged." In five patients the weight and height were not obtainable from the charts and the cardiothoracic ratio was substituted as a measurement with complete realization of its limitations. A ratio of more than 1:2 was considered abnormal. Variations due to differences in phase of respiration were checked by the level of the diaphragm.

An obvious limitation in a study such as this is the inability to state exactly that enlargement is present in some borderline x-ray films. Some teleroentgenograms with normal measurements gave the impression of enlargement because of the configuration of the heart; whenever possible this was checked by fluoroscopy and the decision regarding enlargement was made on the basis of the latter finding. Particular attention was paid to the progressive changes in the patient's own series of x-ray films and occasionally enlargement definitely took place even though the percentage of deviation from the predicted value remained within normal limits.

RESULTS

1. *Sex and Age.* Of the 45 patients studied, 25 were females and 20 males with ages ranging from 29 to 66 years at the time of first observation.

2. *Period of Observation.* When grouped into five year periods the following tabulation was obtained:

Observation for	5 to 9 years	—18 patients
	10 to 14	—14
	15 to 19	— 9
	20 plus	— 4

3. *The Size of the Heart in Relation to the*

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Duration of Hypertension, Congestive Failure, Myocardial Infarction and Weight Loss. a. Duration of Hypertension and Length of Observation: The relationship of the size of the heart to the duration of hypertension from its discovery may be observed in table 1. In the absence of any previous record of hypertension at this hospital or in any other institution, the date of discovery of hypertension was taken from the time of first observation at our clinic. The duration of hypertension was undoubtedly longer than the period of observation since all but two of the patients had hypertension when first seen.

TABLE 1.—*Relationship of Size of Heart in Roentgenogram to Duration of Hypertension in 45 Patients*

Years from discovery of hypertension*	Normal at first observation with subsequent enlargement		Normal at first observation with no subsequent enlargement	Enlarged at first observation (T.D. +11% or more)
	T.D. +11% to +14%	T.D. +15% or more		
1 to 5	4	2	0	1
6 to 10	3	3	4	5
11 to 15	1	1	4	7
16 to 20	1	3	3	3
Total	9	9	11	16

* With long intervals between x-ray examination, time of enlargement was taken as the last year of normal measurement plus one.

TABLE 2.—*Effect of Loss of Weight on Size of Heart in 12 Patients with Essential Hypertension*

Name	Degree of Hypertension	Weight loss	Time	Change in transverse diameter	Deviation from predicted transverse diameter (%)	
					Before wt. loss	After wt. loss
		lbs.	*yrs.*	*cm*		
A. B.	M	40	3	−2.4	+3	−2
E. H.	M	40	8	0	−8	+4
G. M.	M & L	30	5	+1.0	−4	+14
J. M.	M & L	(20)	(10)	(+1.8)	(+6)	(+27)
		(15)	(4)	(+1.2)	(+27)	(+34)
		35	14	+3.0	+6	+34
E. R.	H	24	1	−0.2	+2	+7
A. O.	M	20	4	−1.0	+5	+6
C. W.	M & L	30	5	0	0	+7
M. W.	M	27	8	+2.9	−1	+33
P. Mc.	M	22	5	−1.0	+10	+12
P. M.	H	20	7	+3.9	+10	+50
C. S.	M & H	20	3	−0.8	+11	+11
S. S.	M & H	32	5	+2.2		

H—High (diastolic higher than 120 mm Hg).
L—Labile.
M—Moderate (diastolic pressure 90 to 120 mm. Hg).

Eleven of the 45 patients had normal cardiac measurements throughout observation covering a period of 5 to 20 years (table 1). Seven of these patients were observed between 10 and 20 years, and four were observed for 5 to 10 years. Of those patients showing enlargement sometime during the course of this observation, 18 had normal measurements when hypertension was discovered and the measurements remained normal for 1 to 20 years subsequently. Six of these 18 had normal measurements from 5 to 10 years; six had normal measurements for more than 10 years. Of the total of 45 patients, 10 had normal measurements for 5 to 10 years of observation, and 13 had normal measurements for more than 10 years of observation.

TABLE 3.—*Duration of Life After Appearance of Cardiac Enlargement in Six Patients*

Heart size	Patients	Years from discovery of hypertension to cardiac enlargement	Cause of death	Years from cardiac enlargement to death
Enlarged subsequent to discovery of hypertension	A. P.	6	CHF	1
	C. R.	18	Myocardial infarct	2
	J. B.	8	CHF	3
	C. S.	3	Pneumonia	8
	A. A.	4	Sudden	8
	E. R.	6	Unknown	3

CHF—Congestive heart failure.

b. Congestive Heart Failure: Fourteen patients were in congestive heart failure at some time during observation. Five of these 14 patients had normal heart measurements prior to and following congestive heart failure; in three the heart measurements were normal for one to four years afterward. Nine of the 14 had enlargement at the time failure first appeared and six of these showed subsequent progressive enlargement.

TABLE 4.—*Cases of Special Interest*

Name	Sex	Age at 1st obs.	Dur. of hyp. fr. discovery to last obs.	1st CHF fr. disc. of hypertension	Heart size fr. disc. of hypertension		Myoc. Inf.	Ang. Synd. yrs.	Ass. cond.	Status last obs.*	Comments
					yrs. obs.	% dev. fr. pred. norm.					
								fr. disc.			
M. B.	M	51	15	N	0	+24	N	N	Pul., F & E	A, IIB†	1) Marked cardiac enlargement without significant change in size for 15 yrs.
					3	+20					2) No great limitation of physical capacity.
					4	+17					
					6	+24					
					9	+24					
					15	+25					
M. C.	F	66	11	at 8 yrs	0	+15	N	at 10 yrs	N	A, Ang. Syn., IIIC, mild CHF	Sudden increase in heart size and CHF accompanying the onset of auricular fibrillation.
					1	+11					
					3	+10					
					8	+9					
					9	+36					
					11	+36					
F. G.	M	55	21	N	0		N	at 20 yrs	Chr., Bronch., LBBB, 20 yrs	A, Ang. Syn., LBBB, IIIC	Presence of LBBB for 20 yrs. with only moderate restriction of physical capacity.
					8	+16					
					11	+15					
					13	+18					
					14	+15					
					16	+12					
					17	+21					
E. H.	F	67	18	N	6	−8	N	at 14 yrs	N	A, Ang. Syn., IIC	1) Long survival from discovery of hypertension.
					7	−5					2) Long standing hypertension with normal heart size.
					9	0					3) A normotensive period (from 7th–11th yrs.) during course of essential hypertension.
					11	−9					
					13	0					
					14	+4					
					15	+4					
					17	0					
					18	+3					

J. F.	M	65	13	N	2 3 4 6 10 13	+25 +25 +25 +25 +25 +25	N	at 11 yrs	LBBB, 13 yrs	A, Ang. Syn., LBBB, IIC	A markedly enlarged heart, remaining relatively stationary for 13 yrs. and the presence of LBBB for a similar period.
J. M.	F	65	15	N	0 1 5 7 10 11 14	+6 +3 +3 +21 +23 +30 +34	at 6	at 2 yrs	Ca of Breast at 4	A, Ang. Syn., IIID	Marked increase in heart size following a myocardial infarction.

* A = Alive CHF—Congestive Heart Failure
D = Dead LBBB—Left Bundle Branch Block
L = Lost Pul. F and E = Pulmonary Fibrosis and emphysema.
† According to criteria of the New York Heart Association.

c. Myocardial Infarction: Six of the 45 patients had myocardial infarction at some time during the period of observation. Two had normal heart measurements at the time of infarction and both maintained normal measurements for three years thereafter. Three had definite enlargement at the time of myocardial infarction. One had slight enlargement after infarction but there was no knowledge of his previous status.

d. Weight Loss: Table 2 summarizes the pertinent data. In seven patients the transverse diameter remained constant or decreased as much as 2.4 cm., but six of these had a probably insignificant change of 1 cm. or less. The weight loss in these seven patients occurred over a period of one to eight years with the minimum loss being 20 pounds. With a comparable loss of weight, five patients had an increase of transverse diameter between 1.0 cm. and 3.0 cm. over a period of 5 to 14 years. Complicating factors, such as congestive heart failure, myocardial infarction or auricular fibrillation did not occur during the period of weight loss.

e. Time and Mode of Death: The data are summarized in table 3. Seven patients in this series of 45 died. Six of the seven had definite cardiac enlargement prior to death; information on the seventh was incomplete.

4. Cases of Special Interest. Six patients were selected for individual comment (table 4) because of unusual features.

Discussion

According to some investigators[2, 3] the measurement of the transverse diameter of the heart, when used in conjunction with prediction tables based on height and weight, yields an index which is probably the simplest and subject to the fewest errors, provided a uniform technical procedure is used. In support of the radiographic method has been the finding of a mutual relationship when the anatomic and roentgenographic measurements were correlated.[3] In our study single examinations were frequently found inconclusive as to the presence or absence of cardiac enlargement. However, when x-ray films were taken at intervals, a comparison revealed significant changes in size in many, indicating cardiac enlargement. The chief difficulty in using the measurement of the mean transverse diameter was the inability to distinguish between early left ventricular enlargement and a normal sized but transversely placed heart. Although the shape and configuration of the heart were helpful, recourse had to be made to fluoroscopy for the differentiation. When an over-all comparison was made between x-ray film measurement and fluoroscopy a 20 per cent variation was found, with fluoroscopy often indicating early left ventricular enlargement in the presence of normal x-ray film findings. As one would expect, the difficulty occurred chiefly in those patients with borderline measurements.

It must be realized that regardless of which procedure one uses for determining cardiac enlargement the criteria will be subject to criticism. This is true even for gross and microscopic anatomic measurements for the determination of muscle fiber hypertrophy. Clinical methods admittedly fail to determine the earliest stages of cardiac enlargement. For this reason, we have concerned ourselves chiefly with changes in the size of the heart by radiographic determination rather than with any statement regarding the size of the heart at a particular stage of hypertensive disease.

It is apparent from an analysis of the data (table 5) that the changes in the size of the heart in the course of hypertension do not fit any fixed pattern. Although the majority of hearts manifested progressive enlargement once the hypertensive process was discovered, there were a number of patients whose hearts remained unchanged in size for as long as 10 to 20 years after the discovery of hypertension. (table 6). This occurred regardless of whether the heart was normal or enlarged at the time of first observation. On the other hand, some patients developed sudden enlargement sometime during the course of observation. Congestive heart failure and the onset of auricular fibrillation appeared to be associated with cardiac enlargement, although in other patients the precipitating factor could not be ascertained.

In agreement with the investigations of others[4, 5] this study failed to demonstrate a direct relationship between the size of the heart

and the duration of hypertension. It was not unusual to find absence of cardiac enlargement even after long periods of sustained hypertension. Others[6, 7] have also failed to find cardiac enlargement after prolonged hypertension in some patients. Although the series was small, it did appear that acute myocardial infarction might occasionally result in sudden cardiac enlargement, but no definite correlation between myocardial infarction and the size of the heart could be made. It is of interest to note that congestive heart failure complicated by acute myocardial infarction may occur in the presence of a heart of normal size or with minimal enlargement.

Because of the small number of patients in the present series, no significance can be attributed to the percentage incidence of myocardial infarction in the course of hypertensive heart disease. The true incidence would be extremely difficult to ascertain since many patients with hypertension, previously asymptomatic, may die with their initial myocardial infarct or may have subsequent normotensive readings and therefore not be recognized as having hypertensive disease.

TABLE 5.—*Summary of Changes in the Size of the Heart in the Course of Essential Hypertension Observed for Five to Twenty years*

Size of heart at time of discovery of hypertension	Size of heart stationary	Progressive enlargement	Sudden enlargement	Total
Normal	11	16	2	29
Enlarged.....	7	8	1	16
Total	18	24	3	45

With regard to the presence of congestive heart failure, there were normal heart measurements in five patients with or subsequent to heart failure. In some of these, the heart remained normal for as long as four years after congestive heart failure occurred. This would indicate that the presence of a normal sized heart by x-ray examination does not exclude the diagnosis of congestive heart failure. This conclusion is confirmed by pathologic evidence gathered by others who found hearts of normal weight in the presence of congestive heart failure following long standing hypertension.[6] Since, in this last mentioned study, muscle fiber hypertrophy was found, it would appear that the criteria for "cardiac enlargement" require further clarification both clinically and pathologically. The relatively small incidence of patients with congestive heart failure in this series, may be attributed to the fact that not all patients were followed to time of death.

With regard to the effect of weight loss on cardiac size, a review of the data revealed that weight loss of 20 to 40 pounds did not result in a decrease of the transverse diameter of the heart. A recent clinical pathologic correlation reported by others[6] tends to confirm this clinical finding. This observation is of particular interest since it differs from the findings in normotensive subjects under conditions of malnutrition and semistarvation in which the heart has been found to decrease in size in line with the general loss of body weight.[8] It would seem that the factor of hypertension tends to prevent the heart taking part in the general tissue loss which occurs in starvation.

TABLE 6.—*Duration of Unchanged Cardiac Size in Twenty-one Patients with Essential Hypertension*

Size of heart at time of discovery of hypertension	Number of patients	Years of observation
Normal	1	1 to 5
	5	6 to 10
	4	11 to 15
	3	16 to 20
Enlarged	1	1 to 5
	4	6 to 10
	3	11 to 17

It is difficult to evaluate the finding of cardiac enlargement in all of our patients who died.

The finding in 16 patients having hypertensive vascular disease with cardiac enlargement for more than 10 years is encouraging, but since this was a selected study, the significance of this finding may be limited. It does not militate against the statistical contention that essential hypertension is a serious disease curtailing the life span.

Caution has been stressed by others when evaluating prognosis in patients with hypertensive disease. Reliance on single measure-

ments or on any single sign has been found unreliable. This study would also indicate that prognosis based upon the size of the heart alone is not possible. The finding of a long life span with marked cardiac enlargement and the presence of a normal size heart following congestive heart failure would indicate the unreliability of this factor in making a prognosis.

Summary and Conclusion

1. The changes in the size of the heart as measured by teleroentgenogram in the course of essential hypertension in 45 patients have been studied and the following conclusions reached: (a) From the discovery of hypertension the majority of patients (24) showed progressive cardiac enlargement regardless of the initial measurements. (b) In 18 patients the size of the heart remained stationary for as long as 10 years or more. (c) In three instances the heart manifested sudden enlargement sometime during the course of observation and continued to progress in size regardless of the initial measurements.

2. With regard to the effect of factors such as congestive heart failure, myocardial infarction, degree of hypertension and weight loss, the following facts were noted: (a) Congestive heart failure was found to occur with normal heart measurements. This was observed in 5 of 14 patients. (b) No uniform relationship could be established between the size of the heart and myocardial infarction, although in some patients myocardial infarction was followed by sudden cardiac enlargement. (c) Weight loss of 20 to 40 pounds did not affect a reduction in the size of the heart. d) No direct relationship could be established between the duration and the degree of hypertension and the size of the heart. The finding of normal cardiac measurements in the course of hypertension of a decade or more was not unusual. (e) Marked cardiac enlargement was present in four patients for 10 or more years with little functional limitation.

3. Prognosis on the basis of the size of the heart alone was found to be unwarranted. Cardiac size is only one facet in the clinical picture. The inclusion and evaluation of all factors is important in making a prognosis in essential hypertension.

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Quantitative Studies in Man of the Cardiovascular Effects of Reflex Vagal Stimulation Produced by Carotid Sinus Pressure

I. Localization of an Increased Effect in a Patient with Angina Pectoris

By ARTHUR J. LINENTHAL, M.D.

with the technical assistance of Virginia Marcus, B.S.

In a two year period the effect of carotid sinus pressure on auriculoventricular conduction in a 70 year old man with angina pectoris increased markedly. At first, right carotid sinus pressure gave only P-R interval prolongation. Two years later, pressure on either side produced dropped beats. The maximum effect on the sinoauricular rate remained the same. No other change could be detected in the patient's heart during this period. The site of the cause of the increased vagal effect was either in the intrinsic cardiac nerves to the atrioventricular node or in the node itself.

MARKED cardiac effects due to reflex vagal stimulation are frequently observed following carotid sinus pressure in patients with various diseases, especially coronary artery disease.[1, 2] However, the segment of the reflex arc responsible for hyperactivity of the reflex has not previously been demonstrated, except in the occasional case showing a lesion in the neck near the carotid sinus.[1]

Repeated studies of the carotid sinus reflex over a two year period in a patient with angina pectoris, particularly suitable for such studies, indicated that the site of an increased vagal effect was in the heart; either in the auriculoventricular node or in the intrinsic cardiac nerves to that node. Initially, right carotid sinus pressure had no effect on the auriculoventricular node, whereas left carotid sinus pressure produced P-R interval prolongation; two years later pressure on either side produced dropped beats. During the entire period of observation, the maximum effect on the sinoauricular rate from pressure on either side remained the same.

The presentation and analysis of our observations in this patient form the basis of the present report.

OBSERVATIONS

The patient, N. S. (BIH #17498), a 70 year old man (in 1948), had been known to have attacks of angina pectoris for about 10 years. These attacks were usually precipitated by exertion and were characterized by a squeezing substernal pain radiating down the left arm, relieved by nitroglycerin and by rest. Similar attacks could be brought on readily by a two step exercise test.[3]

The detailed observations reported here were made on six days during a three month period (April to June) in 1948 and on six days during a three month period (June to August) in 1950. With the patient in a sitting position, a continuous electrocardiogram (lead II) was taken immediately before, during and immediately after the application of pressure to either the right or the left carotid sinus. Pressure was applied 24 times in 1948, 11 on the right and 13 on the left; 54 times in 1950, 32 on the right and 22 on the left. At least three or four minutes were allowed to elapse between successive pressure tests on the same day; this interval has been found to be well beyond the time required for the electrocardiographic changes produced by pressure to disappear. In 1948 each pressure was applied for about five seconds; in 1950 for exactly

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three seconds. In 1948 the observer stood behind the patient and, with his fingers over the site of the maximum pulsation, massaged the neck and the carotid sinus vigorously toward the vertebral column. In 1950 manual pressure was applied similarly in some instances; in other instances a measured-pressure device which will be described elsewhere[4] was used. The manual pressures in 1948 and 1950 were of approximately the same intensity; the measured pressures in 1950 varied over a wide range, generally being less intense than the manual ones.

Each P-R interval of the electrocardiogram was paired with the preceding P-P interval; both intervals were measured to the nearest 0.01 second. Five to ten successive P-P intervals immediately before each pressure, varying usually by no more than 0.03 second, and the corresponding P-R intervals, usually showing no variation, were used as controls to determine the changes produced by that pressure. For the purposes of this report only maximum changes in P-P and P-R intervals are considered. Data not included here indicated that the greatest P-R interval prolongation before the occurrence of dropped beats in this patient was 0.10 second. Further increase in this effect could not be measured; dropped beats, therefore, have been grouped as indicating the maximum increase in auriculoventricular conduction time.

On several occasions the patient noted mild, very transient dizziness in association with carotid sinus pressure. This occurred particularly in 1950 when slowing of the sinoauricular rate together with a dropped beat sometimes produced ventricular asystole for as long as three seconds. He gave no history, however, of similar spontaneous attacks of dizziness.

TABLE 1.—*Maximum Effects of Right and Left Carotid Sinus Pressure on the P-P and P-R Intervals*

Right						Left					
P-P			P-R			P-P			P-R		
Cont.*	CSP†	Inc.‡	Cont.	CSP.	Inc.	Cont.	CSP.	Inc.	Cont.	CSP	Inc.
1948											
	(sec.)			(sec.)			(sec.)			(sec.)	
.84	1.42	.58	.15	.15	0	.76	1.17	.41	.15	.18	.03
.78	1.35	.57	.15	.15	0	.82	1.20	.38	.15	.21	.06
.78	1.29	.51	.15	.15	0	.76	1.13	.37	.15	.19	.04
.90	1.39	.49	.15	.15	0	.85	1.19	.34	.15	.25	.10
.92	1.35	.43	.15	.15	0	.94	1.23	.29	.15	.23	.08
.92	1.33	.41	.15	.15	0	.85	1.13	.28	.15	.22	.07
1950											
.91	1.49	.58	.15	DB§	—	.87	1.33	.46	.15	DB§	—
.85	1.26	.56	.15	DB	—	.85	1.15	.30	.15	DB	—
.82	1.35	.53	.15	DB	—	.85	1.35	.30	.15	DB	—
.74	1.22	.48	.15	DB	—	.87	1.17	.30	.15	DB	—
.84	1.30	.46	.15	DB	—	.85	1.13	.28	.15	DB	—
.80	1.19	.39	.15	DB	—	.86	1.08	.22	.15	DB	—
.77	1.15	.38	.15	DB	—	.85	1.04	.19	.15	DB	—
.90	1.27	.37	.15	DB	—	.87	1.05	.18	.15	DB	—
						.89	1.03	.14	.15	DB	—

* Control before pressure.
† Maximum during carotid sinus pressure.
‡ Maximum minus control.
§ Dropped beat.

RESULTS

Table 1 shows the maximum effects of right and left carotid sinus pressure on the rate of impulse formation in the sinoauricular node (change in P-P interval) and on the duration of auriculoventricular conduction (change in P-R interval).

In 1948 right carotid sinus pressure slowed the rate but did not increase auriculoventricular conduction time. Left carotid sinus pressure in 1948 produced prolongation of the P-R interval as well as slowing, although dropped beats

were never observed. In 1950, however, dropped beats were readily produced following either right- or left-sided pressure. The maximum slowing of rate, on the contrary, from pressure on either side remained the same in both years.

Discussion

Various factors relevant to the interpretation of these data are considered below. The conclusion is reached that the increased effects of carotid sinus pressure in 1950 as compared to 1948 must have been due to an increased sensitivity to reflex vagal stimulation of the auriculoventricular node or of the postganglionic fibers to that node.

There was no variation in the intensity of the pressure in the two periods to account for the increased effect. The maximum pressure applied in 1950 was of about the same intensity as in 1948. The fact that the maximum effect on the rate was the same in both years confirms the fact that the intensity of maximum vagal stimulation reaching the heart from right and left carotid sinus pressure remained the same.

Since the change in our patient between 1948 and 1950 involved only the auriculoventricular node, it was undoubtedly not related to a difference in sympathetic inhibition[5] accompanying the reflex vagal stimulation. Variations in this mechanism would be expected to affect the sinoauricular node as well as the auriculoventricular node.

Local alteration in either one or both carotid sinuses can similarly be excluded because the increased effect involved only the auriculoventricular node and not the sinoauricular node.

It is likewise clear that slowing of the sinoauricular rate had no causal relation to the increase in auriculoventricular conduction time. The lack of correlation between the P-P and the P-R intervals has been described by Schlamowitz.[6] Our observations confirm this: following right-sided pressure in 1948, with P-P intervals ranging from 0.78 to 1.42 seconds, the length of the P-R interval was constant at 0.15 second.

The possibility of crossing of stimuli from either right or left carotid sinus can be excluded as a factor in the increased vagal effect in this patient. The data obtained in 1948 indicate that there was no significant crossing of stimuli to the auriculoventricular node from the right to the left. Left-sided pressure produced a marked effect on this node, that is, definite P-R interval prolongation. However, no effect on the P-R interval was produced by right-sided pressure at that time. This indicates that, if any stimuli did cross from right to left, their intensity was below the threshold of the auriculoventricular node. Our data permit no conclusions regarding crossed effects on the rate. However, even if stimuli of sufficient intensity to affect the sinoauricular node did cross, equally in both directions and to the same extent in both periods, the following interpretation of our data is not altered.

On the basis of the above considerations, it must be concluded that the observed increase from 1948 to 1950 in the effects of right and left carotid sinus pressure on the auriculoventricular node were due to alterations in that part of the reflex arc common to the two sides: the cardiac postganglionic fibers going to that node, or the node itself.

Localization of the increased effects of carotid sinus pressure on the heart, frequently observed in older individuals, particularly those with evidence of coronary artery disease,[1, 2] has not heretofore been definitely established. Nathanson[7] reasoned that the cause must be somewhere on the efferent side of the reflex arc, because of the variation in the relative magnitude of the cardioinhibitory and vasodepressor effects of carotid sinus pressure from one individual to another. Sigler[8] suggested, without supporting data, that changes in the cardiac ganglia might explain the reflex hyperactivity.

Increases in the cardiac effects of carotid sinus pressure have been described in association with a number of conditions, including exacerbation of angina pectoris,[9] congestive heart failure,[10] acute myocardial infarction,[11, 12] and the administration of several drugs, particularly digitalis glycosides.[13] None of these were involved in our patient, whose clinical condition over the two year period remained unchanged. A number of electrocardiograms taken between 1948 and 1950 were identical and, except for left axis deviation, were within normal limits. The blood pressure ranged between 130/70 and

190/90 with no constant trend. Red blood cell counts, hemoglobin determinations and urine examinations were repeatedly normal, and the Hinton test was negative.

Increased sensitivity as a result of anoxia may offer an explanation of the observations made in our patient. Coronary arteriosclerosis, undoubtedly the cause of his angina pectoris,[14] is associated with diminished blood flow to the heart and localized anoxia.[15] Changes in sensitivity have been seen in nerves subjected to anoxia[16] and, accordingly, in this patient, the threshold of the intrinsic nerves to the auriculoventricular node may have been lowered. Other studies[4] in this patient and in other patients have shown that only a small increase in sensitivity may be required to increase markedly the effect of a given stimulus. It is of interest that degenerative changes have been described, most recently by Hermann,[17] in the intrinsic cardiac ganglions of patients with coronary artery disease.

Similar considerations could apply to the nodal tissue. In this connection it should be noted that the control P-R interval, the same in 1948 and 1950, was within normal limits.

Summary

In a two year period the effect of carotid sinus pressure on auriculoventricular conduction in a 70 year old man with angina pectoris increased markedly. At first, right carotid sinus pressure had no effect, whereas left carotid sinus pressure gave some P-R interval prolongation. Two years later, pressure on either side produced dropped beats. The maximum effect on the sinoauricular rate from pressure on either side remained the same. No other change could be detected in the patient's heart during this period.

The data indicate that the site of the increased vagal effect was either in the intrinsic cardiac nerves to the auriculoventricular node or in the node itself.

Acknowledgment

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Mercurial Diuresis in Edematous Individuals

By GERSON T. LESSER, M.D., MARCELLE F. DUNNING, M.D., FREDERICK H. EPSTEIN, M.D. AND EUGENE Y. BERGER, M.D.

The electrolyte and water losses in 75 instances of diuresis following Mercuhydrin were studied in 17 edematous patients. The loss of potassium was appreciable following exhibition of the drug to patients who retained their dietary sodium almost completely. Occurrence of such clinical symptoms as weakness, nausea, and ventricular premature contractions might be attributed to this loss of potassium. The fluid lost by mercurial diuresis was isotonic with body fluids. The chloride concentration was fairly constant at 151 mEq. per liter. The concentrations of sodium and potassium were more variable, the average concentrations being 97 and 35 mEq. per liter, respectively. Loss of water and electrolyte in these concentrations leaves the patient in relative alkalosis, with a loss of intracellular potassium and a gain in intracellular sodium.

THE effect of mercurial diuretics on the renal excretion of electrolytes has been thoroughly investigated in the dog and in the normal man.[1–4] The electrolyte losses in the edematous patient, however, have been studied less extensively.[4–7] There is general agreement that in both the normal individual and in the edematous patient the diuresis is predominantly one of sodium and chloride. There is also agreement that potassium excretion is not increased in normal individuals while in the edematous patient an examination of the reported data reveals potassium loss of varying magnitude.[4–8] The present study was designed to extend the information concerning the relative losses of sodium, potassium and chloride following administration of a mercurial diuretic in edematous patients and to assess the changes in body fluid compartments resulting from these losses.

METHODS

Twenty-four hour losses of water and electrolyte were measured following the administration of Mercuhydrin to 13 patients with congestive heart failure and to 4 with ascites due to cirrhosis of the liver. In all, 75 diureses were studied in these 17 patients. Although the daily intake of sodium was approximately 70 mEq., 24 hour specimens prior to the administration of Mercuhydrin all contained less than 10 mEq. and 55 of the 75 contained less than 2 mEq. of sodium. A period of at least four days was allowed between injections of the mercurial diuretic in the same patient. The patients with congestive heart failure were all receiving maintenance doses of digitalis.

The effect of adjuvants to the mercurial salts was also observed. Ammonium chloride, when used, was administered continuously as nonenteric-coated tablets in daily doses of 100 mEq. Ammonium carboxylic resin, when used, was given in dosage of 45 Gm. per day.* The exchange capacity of this resin in terms of removal of sodium and potassium from the body was estimated as 2 mEq. per Gm.

Ammonium chloride induces acidosis by the addition of excess anion to the body pool; ammonium cation exchange resin, by depletion of body base, particularly potassium.[9] Whether or not acidosis per se potentiates the diuresis is unknown,[10] but in either instance the adjunct therapy potentiates the mercurial diuresis.

Urine was collected during two consecutive 24 hour periods. At the beginning of the second period 2 or 3 ml. of Mercuhydrin was administered intravenously. In order to express the electrolyte and water losses due to the Mercuhydrin the electrolyte and water excretion during the 24 hours prior to the injection was subtracted from the excretion during the 24 hours following mercurial administration. It was assumed that extrarenal water losses were the same on both days. The electrolyte and water loss due to the mercurial injection is regarded as a bloc of fluid which is called, for want of a better term, the "diuretic urine," and its components, "diuretic

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During the course of the work one of the authors (F. H. E.) was a Fellow of the New York Heart Association.

* The resin used (Amberlite IRC-50 of Rohm and Haas Co., Philadelphia, Pa.) was kindly packaged and supplied in the ammonium form by Smith, Kline and French Laboratories, Philadelphia, Pa.

water, sodium, potassium and chloride." Because of the inherent variability in daily water and electrolyte excretion, the control urine does not precisely represent the electrolyte excretion on the day of the mercurial if a diuretic had not been administered. This error may be appreciable in small diureses but is minimized in larger ones. In this report, therefore, only those diureses have been included in which there was an increase of at least 1000 cc. of urine over the previous day's output.

Sodium and potassium were determined in an internal standard flame photometer,[11] chloride by the method of Wilson and Ball,[12] ammonium according to Summerson's modification of the Van Slyke and Cullen procedure.[13]

The mean increase in urinary chloride (diuretic chloride) was 425 mEq. Chloride did not appear in the urine exclusively as the sodium salt. The average diuretic sodium was 281 mEq., the average diuretic potassium 92 mEq. Diuretic potassium ranged from 7 to 200 mEq. The largest potassium losses occurred in those diureses where the patient received ammonium chloride. The patients receiving resin did not lose as much potassium in the urine as those receiving ammonium chloride, but they were, at the time of mercurial administration, losing potassium in the stool.[9]

TABLE 1.—*Electrolyte Excretion in Diuretic Urine Following Mercuhydrin*

Adjunct therapy	No. of observations	Mean 24 hour losses				Mean concentration in diuretic urine			
		Diuretic water	Diuretic chloride	Diuretic sodium	Diuretic potassium	Chloride	Sodium	Potassium	Sodium and potassium
		ml.	*mEq.*	*mEq.*	*mEq.*	*mEq./L*	*mEq./L*	*mEq./L*	*mEq./L*
None	26	2396	359	245	77	151	99	36	135
Ammon. chloride	16	2858	440	266	128	157	90	49	139
Resin	33	3215	471	314	87	149	99	28	127
Mean	75	2855	425	281	92	151	97	35	132
σ*		1127	152	135	44	21	25	15	22
100 σ/m		40	36	48	40	14	26	43	17

* $\sigma = \sqrt{\frac{\Sigma x^2}{N} - \bar{x}^2}$.

OBSERVATIONS

Seventy-five diureses following the administration of Mercuhydrin were studied in patients who were accumulating fluid. The mean increase in urinary volume over the previous day's excretion (diuretic water) for the entire group was 2855 ml. (table 1). There is no significant statistical difference between the mean diuretic water in the groups with and without adjunct therapy (ammonium chloride or resin). Since diuretic volumes under 1000 cc. have been excluded from this series, a comparison of these mean volumes should not be interpreted as meaning that the adjunct therapeutic agent was ineffective. Ammonium chloride or resin usually potentiated the response to Mercuhydrin in a given patient in whom diuretic water would have been less than 1000 cc. without adjunct therapy. Moreover, cation exchange resin often potentiated the diuresis when ammonium chloride failed to do so.

The relationship of sodium and potassium losses to chloride loss is illustrated by 20 diureses which were selected from the group to cover the range of chloride losses (fig. 1). Although most of the chloride may be accounted for as the sodium and potassium salt, the equivalents of chloride are usually in excess of the equivalents of sodium and potassium. There is probably a small increase in the excretion of other cations to balance the diuretic chloride excretion. An attempt was made to account for this relative cation deficit. The pH of the urine varied less than ±0.5 pH units between the control and diuretic day in 37 of 62 observations. In the other 25 observations the pH shifted 1 to 2 units to the acid side. A shift of 1 to 2 pH units at pH values of 5.0 or 6.0, however, contributes only negligibly to free hydrogen ions in the urine. In 27 of 62 observations the ammonia excretion was the same (±30 mEq.) on the control day as on the day of the

n ercurial, but increased more than 30 mEq. in 3 diureses. It may be that calcium and magnesium appear in increased amounts as well.[4, 6]

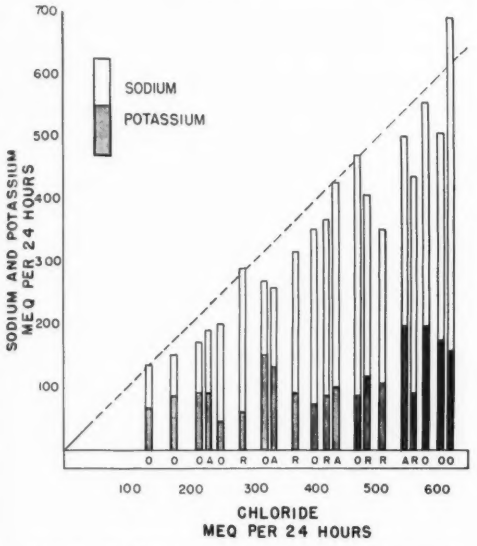

FIG. 1.—Sodium, potassium and chloride excretion following Mercuhydrin (increase over previous 24 hours). 0, no adjunct; A, ammonium chloride; R, resin.

When the chloride loss is plotted against water loss for the 75 mercurial injections, it becomes clear that the chloride concentration is quite constant for all diureses and independent of the extent of the diuresis and of the adjunct therapy (fig. 2). The mean concentration of chloride in diuretic urine was 151 mEq. per liter ±14 per cent* (table 1). When sodium and potassium losses are compared with water loss it was found that the mean sodium concentration was 97 mEq. per liter and the mean potassium concentration 35 mEq. per liter, but the individual values varied considerably (±26 and ±43 per cent respectively). The sum of the sodium and potassium concentrations, however, had about the same variability (±17 per cent) as the chloride.

When chloride is removed from the body in concentration of 151 mEq. per liter, sodium in concentration of 97 mEq. per liter and potassium in concentration of 35 mEq. per liter, changes in the plasma concentration of the electrolytes may be anticipated. Plasma sodium, potassium and chloride were therefore determined at the time of mercurial administration and again 24 hours later in 13 diureses in 6 patients (table 2). Plasma chloride fell in every instance[14–18]; the average fall was 5.1 mEq. per liter. Plasma potassium remained unchanged or fell slightly. Sodium values did not change significantly.

* 100 σ/mean.

TABLE 2.—*The Effect of the Electrolyte Losses following Mercuhydrin on Plasma Electrolyte Concentrations*

Diuresis	Adjunct therapy	Change in plasma sodium concentration	Change in plasma potassium concentration	Plasma chloride before Mercuhydrin	Plasma chloride 24 hrs. after Mercuhydrin	Change in plasma chloride concentration	Diuretic water	Diuretic chloride
		mEq./L.	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*ml./24 hrs.*	*mEq./24 hrs.*
1	Ammon. chloride	−1.8	−0.7	110.5	109.2	−1.3	2120	312
2	None	−1.2	0.0	115.0	112.8	−2.2	1490	222
3	Ammon. chloride	−3.8	−0.7	114.8	112.0	−2.8	1840	290
4	None	0.0	−0.3	112.0	109.2	−2.8	2400	344
5	None	0.0	0.0	114.8	111.3	−3.5	1690	222
6	None	−2.6	+0.1	110.8	106.8	−4.0	1340	181
7	None	+1.6	−0.4	104.5	100.2	−4.3	2360	356
8	None	0.0	−0.1	113.5	109.0	−4.5	2040	331
9	Ammon. chloride	0.0	−1.2	111.0	105.5	−5.5	1340	231
10	Ammon. chloride	−4.6	−0.6	116.0	108.0	−8.0	1560	236
11	Ammon. chloride	−1.6	−1.4	103.8	95.5	−8.3	3020	432
12	Ammon. chloride	+3.4	−1.5	104.0	94.5	−9.5	3190	438
13	Ammon. chloride	−1.8	—	108.1	98.3	−9.8	2320	364
Mean		−1.0	−0.5	110.7	105.6	−5.1	2054	304

Discussion

Appreciable potassium losses following mercurial administration have not ordinarily been observed in normal individuals.[1, 4] Edematous patients studied in this laboratory who still have the capacity for excreting a fair proportion of dietary sodium in the urine also do not lose significant amounts of potassium. The present group of patients, who were, however, excreting negligible amounts of dietary sodium in the urine, invariably lost potassium following the use of a mercurial diuretic. The distinction between these two types of reaction to Mercuhydrin was also observed in a single individual who was not included in the series because she did not consistently excrete less than 10 mEq. of sodium per day. During the course of congestive heart failure in this patient there were periods when more sodium was excreted in the urine than at others. When, on a diet containing 70 mEq. of sodium, daily urinary sodium excretion was 40 to 60 mEq., there was little change in potassium excretion (−17 to +20 mEq.) following Mercuhydrin. On other occasions on the same diet, when the daily urinary sodium was less than 10 mEq., the diuretic potassium ranged from 60 to 150 mEq.

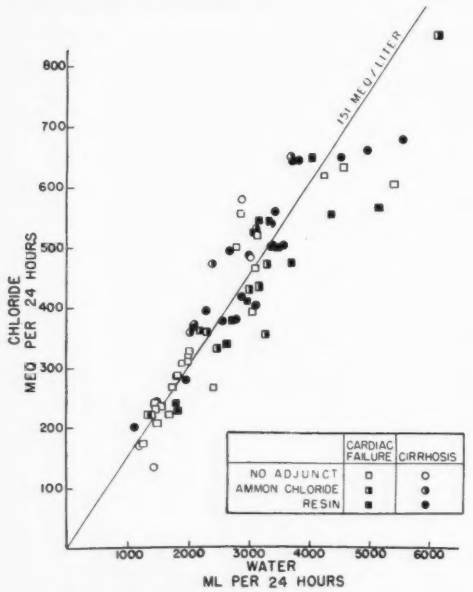

Fig. 2.—Chloride and water excretion following Mercuhydrin (increase over previous 24 hours).

In view of these considerable losses of potassium, in one instance 200 mEq. (7 per cent of the total potassium content of the body[19]), the reasons for some of the untoward signs and symptoms which may follow the injection of mercurial diuretics should be reconsidered. The weakness and nausea which sometimes follow a large diuresis have usually been attributed to sodium depletion[20, 21] but may be related to the loss of potassium. The occurrence of arrhythmias after mercurial diuresis in digitalized patients, usually attributed to mobilization of digitalis from edema fluid[22–24] may also be due to potassium depletion. A relationship between digitalis toxicity and available potassium has been reported.[25, 26] Additional evidence for a relationship between the occurrence of arrhythmias and potassium depletion has been observed in this laboratory. Patients in congestive heart failure receiving ammonium or hydrogen cation exchange resin lose large amounts of potassium in the stool. When these patients are on maintenance doses of digitalis, it is not uncommon for them to develop premature contractions. The abnormal rhythm may be terminated by administering potassium or by withdrawing the resin or digitalis.[27]

It has been observed (fig. 2) that the mean concentration of chloride in the diuretic urine was 151 mEq. per liter. This concentration of chloride is essentially isotonic with body fluids.[28, 29] Thus a bloc of fluid has been lost during the diuresis which leaves the tonicity of body fluid unchanged but alters the concentrations of individual ions.

The concentrations of sodium, potassium and chloride in the diuretic urine yield certain information concerning their origin. The concentrations of potassium and of chloride are greater and that of sodium is less in diuretic urine than in extracellular fluid. If all the electrolytes and water came from extracellular fluid alone, it would be expected that plasma chloride and potassium would fall following Mercuhydrin while plasma sodium would rise. The mean fall in plasma chloride was of the magnitude one would expect if water with chloride in a concentration of 151 mEq. per liter is re-

moved from extracellular fluid with a concentration of chloride of 110 mEq. per liter.* Thus the chloride and water loss following Mercuhydrin can be accounted for as originating entirely from extracellular sources. In fact, if significant amounts of water had come from intracellular sources of low chloride concentration, the high concentration of chloride in the urine would be difficult to explain. (The possibility remains that some portion of the water loss may come from intracellular sources of high chloride concentration. Skin has been observed to have an unusually high concentration of chloride.[33])

The fall in plasma potassium, however, is by no means great enough to account for the potassium loss as coming from the extracellular fluid alone. Indeed, the potassium loss in certain diureses was larger than the total calculated amount of extracellular potassium, so that intracellular loss of potassium seems unquestionable. The concentration of sodium in the diuretic urine is less than that in the extracellular fluid and a rise in serum sodium might be expected. Since this was not observed, sodium presumably entered the intracellular fluid in exchange for intracellular potassium, the loss of which has already been indicated. Thus, the mercurial diuresis in a patient who is actively accumulating edema fluid leaves the patient relatively alkalotic, with a loss of intracellular potassium and a gain in intracellular sodium.*

Summary

The electrolyte and water losses in 75 instances of diureses following Mercuhydrin were studied in 17 edematous patients.

The loss of potassium was appreciable following the injection of Mercuhydrin to patients who almost completely retained their dietary sodium. Occurrence of such clinical symptoms as weakness, nausea, and ventricular premature contractions might be attributed to this loss of potassium.

The fluid lost by mercurial diuresis was isotonic with body fluids. The chloride concentration was fairly constant at 151 mEq. per liter. The concentrations of sodium and potassium were more variable, the average concentrations being 97 and 35 mEq. per liter, respectively. Loss of water and electrolyte in these concentrations leaves the patient in relative alkalosis, with a loss of intracellular potassium and a gain in intracellular sodium.

Acknowledgment

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* If the water and chloride losses following the mercurial diuresis are accepted as coming from the extracellular fluid, the volume of the extracellular fluid may be calculated from the relationship

$$P_{Cl_1} \times ECF = P_{Cl_2}\,(ECF - V) - U_{Cl}$$

where P_{Cl_1} is the plasma concentration of chloride at the time the mercurial was administered and P_{Cl_2} is the plasma concentration of chloride 24 hours later; ECF is the volume of extracellular fluid prior to diuresis; V is the 24 hour water loss and U_{Cl} is the chloride loss due to the mercurial (increase of water and chloride over previous day's excretion).

The actual application of this formula to individual experiments is dependent to a great extent upon the accuracy with which plasma chloride can be analyzed. If the analysis is only accurate to 1 mEq. per liter, the error is appreciable when falls in plasma chloride are in the range of 2 to 3 mEq. per liter. The error is proportionately less when the fall in plasma chloride is greater. Analytic errors are minimized when the averages of the group are studied. In applying the above formula to the means of the group the mean extracellular fluid may be estimated as 17 liters. This value is in keeping with the more recent concepts of the size of the normal extracellular space (10 liters),[30-32] 7 liters being a reasonable estimate of the degree of edema.

* On the basis of balance studies in six patients with congestive heart failure, similar conclusions have been recently reported in abstract form by Schwartz and Wallace.[34]

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Norepinephrine and Epinephrine Effect on Renal Hemodynamics

With Particular Reference to the Possibility of Vascular Shunting and Decreasing the Active Glomeruli

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Because increasing evidence suggests that renal ischemia resulting from various stress states plays a major role in the etiology of lower nephron nephrosis, the renal hemodynamic effect of continuous infusions of norepinephrine and epinephrine was studied in dogs. The primary response was a decrease in renal blood flow. As the rate of infusion was increased, a progressive decrease in the number of functioning glomeruli followed. Despite the decrease in renal blood flow, there is no evidence to indicate arteriovenous shunting mechanisms.

HEMORRHAGIC or traumatic shock causes a disproportionate decrease between renal blood flow and cardiac output.[1] This probably represents a protective mechanism for redistribution of blood to more vital areas. Increasing evidence suggests that the renal ischemia thus produced plays a major role in the etiology of lower nephron nephrosis and its attendant renal insufficiency.[2, 3] The alterations in renal hemodynamics under these circumstances may be mediated via the sympathetic nervous system directly or indirectly through the release of epinephrine or other vasopressor substances,[4] since peripheral vasoconstriction due either to sympathomimetic drugs[5–8] or to sympathetic nerve activity[2, 9–11] depresses renal blood flow. Associated with the decrease in renal blood flow there may be a decrease in glomerular filtration rate.[5] Whether or not this is due to a proportional decrease in filtration in all glomeruli, or due predominantly to a decrease in the number of active nephrons, has not been clearly demonstrated. Some investigators have presented evidence to indicate that all glomeruli are continuously perfused with blood and disclaim the possibility that the number of active nephrons can either be increased or decreased in mammals.[12] Others have found evidence to suggest changing numbers of active nephrons.[13–15] Trueta[16] has gone so far as to suggest that under conditions of stress, entire areas of the renal cortex may be shunted out of the circulation due to subcortical or juxtamedullary arteriovenous bypasses. The following report is concerned with an evaluation of the renal hemodynamic effects of epinephrine and norepinephrine. Evidence is presented to indicate that the number of active glomeruli is decreased following the administration of both epinephrine and norepinephrine to dogs, but at the same time there is no evidence to indicate arteriovenous shunting mechanisms.

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METHODS

Two groups of female dogs weighing between 10 and 20 Kg. were studied. One group consisting of nine dogs received a constant infusion of epinephrine (1:100,000 dilution) and seven received an infusion of norepinephrine* (1:100,000 dilution). Four dogs in the first group and three in the second were trained dogs and received no anesthesia. The others were anesthetized with chloralose (100 mg. per Kg.), which seems to have a negligible effect on renal function.[17] A venous catheter was passed through the external jugular vein into the left renal vein with the aid of a fluoroscope so that renal extractions (A−V) of creatinine and paraaminohippurate (PAH) could be determined. Renal plasma flow (RPF) could thus be calculated by the Fick principle (RPF = UV/A−V) using both creatinine and PAH extractions. Glomerular filtration rate (GFR) was determined by the creatinine clearance (GFR =

* Supplied through the courtesy of Mr. Kenneth M. Smoot, Winthrop-Stearns, Inc.

UV/A). Maximum tubular reabsorptive capacity for glucose (Tm_g = GFR × A − UV) was determined. Because glucose has been observed to depress paraaminohippurate extraction[18] by the renal tubules, control values for glomerular filtration rate (creatinine clearance) and renal plasma flow (paraaminohippurate and creatinine extractions) were established before and after glucose was added to the infusing solution. After the control periods were completed, the infusion of epinephrine or norepinephrine was started. The rate was regulated so that there was a definite and sustained increase in systemic blood pressure of 10 to 20 mm. Hg. At least two periods were then run after which the infusion rate was increased and the process repeated. Studies on successive periods during increasing increments of sympathetic effector organ stimulation were thus obtained. Bladder washes of distilled water were used in all but two dogs (Epi. 8 and 9) in group I. In these the ureters were catheterized in order that renal function could be studied on each kidney for comparative purposes. A needle in the femoral artery was connected to a manifold for withdrawing arterial blood samples and recording mean blood pressures. Chemical methods and technics employed have been described.[13]

TABLE 1.—*Response of Kidney Functions to Increasing Rate of Infusion of Intravenous Epinephrine*

Dog No.	UV/min.*	GFR†	RPF‡	RBF§	FF‖	MBP**	RVR††	PAH Ext.‡‡	Hct.§§
	cc./min.	*cc./min.*	*cc./min.*	*cc./min.*		*mm. Hg*			
Epi. 3									
Cont.	1.6	52	196	322	.27	115	.36	76	39.1
Epi. (10γ/min.)	1.2	52	126	229	.41	140	.61	79	45.0
Epi. (30γ/min.)	1.0	37	95	188	.39	170	.90	80	49.4
Off	1.2	50	155	272	.32	80	.29	75	43.0

* UV = Urine Volume—cc./min.

† GFR = Creatinine Clearance—glomerular filtration rate expressed in cc./minute.

‡ $RPF = \text{Renal Plasma Flow} = \frac{UV\ (PAH)}{A\text{-}V\ (PAH)}$.

§ $RBF = \text{Renal Blood Flow} = \frac{RPF}{1\text{-}Hct}$.

‖ $FF = \text{Filtration Fraction} = \frac{GFR}{RPF}$.

** MBP = Mean Blood Pressure—Direct arterial mercury manometer.

†† $RVR = \text{Renal Vascular Resistance} = \frac{MBP}{RBF}$.

‡‡ $\text{PAH Ext.} = \frac{A\text{-}V}{A}$.

§§ Hct = Hematocrit.

RESULTS

During control periods, the values for glomerular filtration rate, renal plasma flow and maximum tubular reabsorption of glucose were all within normal limits.[19] After glucose was added to the infusion, there was a reduction in paraaminohippurate extraction of 10 to 20 per cent.[17] However, after the initial depression there seemed to be no further reduction regardless of the time interval. In a few of the experiments, there was considerable random variation between the creatinine- and paraaminohippurate-determined renal plasma flow.[5] Usually the values obtained by the two different methods agreed within 15 per cent. Values for renal plasma flow as determined by the paraaminohippurate method are the ones used in the present report. When epinephrine and norepinephrine were administered, the renal plasma flow decreased progressively and inversely to the rise in blood pressure as the rate of infusion was increased. Initially, the glomerular filtration rate changed very little resulting in an increased filtration fraction. As the renal plasma flow decreased further, the glomerular filtration rate dropped off equally and progressively. A representative case showing this response is seen in table 1. This pattern

was seen in eight out of nine dogs which received epinephrine, and four out of seven which received norepinephrine. In the others, the filtration fraction did not change significantly since both glomerular filtration rate and renal plasma flow decreased proportionally, both initially and with the more rapid rate of infusion.

The effects of epinephrine (dogs Epi. 1 to Epi. 9) and norepinephrine (dogs Nor. 1 to Nor. 7) on all renal functions studied are summarized in table 2. The results are expressed in percentage of control values considering the control figures as 100 per cent. Values which demonstrated definite changes in renal function but at the same time were most reproducible during successive study periods, were the ones chosen for this table. The relationship between glomerular filtration rate and tubular maximum for glucose is graphed in figure 1. The study periods not included in Table 2 are also included in this graph. There appeared to be no difference in response between anesthetized and unanesthetized dogs, or between left (renal vein catheterized) and right (uncatheterized) kidneys (dogs Epi. 8 and 9).

Depression of the glomerular filtration rate was associated with a parallel decrease in urine volume (UV) and except for a few instances, the ratio GFR:UV was quite constant. During the course of increasing the rate of infusion of epinephrine and norepinephrine, maximal tubular transport of glucose did not seem to be closely related to renal plasma flow, although there were similar directional changes. However, there was a close relationship between the reduction in tubular maximum and glomerular filtration rate with the reduction in the former lagging somewhat behind the latter. This resulted in a slightly reduced, but otherwise constant, GFR:Tm_g ratio. When the tubular maximum is plotted against glomerular filtration rate during increasing rates of infusion there is

TABLE 2.—*Effect of Epinephrine and Norepinephrine on Renal Clearance Studies Expressed as Per Cent of Control Values*

Dog No.*	Urine†	GFR†	RPF†	RBF†	FF†	Tm_g‡	GFR/Tm_g	MBP†	RVR†	PAH Ext.	Hct.†
Epi. 1	80	46	46	52	100	52	88	135	268	—	117
Epi. 2	65	69	64	79	109	78	90	125	158	98	120
Epi. 3	63	71	48	58	144	—	—	148	250	105	126
Epi. 4	40	29	22	34	130	—	—	140	410	106	160
Epi. 5	50	64	51	55	127	70	91	129	238	96	110
Epi. 6	37	47	41	49	112	64	80	136	280	—	125
Epi. 7	20	47	41	44	122	59	78	125	270	106	109
Epi. 8											
L	24	22	20	27	113	23	97	165	610	90	150
R	9	15	15	21	93	15	99	165	790	—	150
Epi. 9											
L	49	60	38	40	158	73	82	145	364	98	113
R	43	48	35	38	133	57	83	155	435	—	113
Mean	44	47	38	45	122	55	88	143	370	100	127
Nor. 1	53	40	43	43	100	—	—	165	340	96	102
Nor. 2	40	70	64	70	110	—	—	125	180	117	115
Nor. 3	67	72	72	75	102	75	96	158	215	—	108
Nor. 4	45	63	61	63	100	—	—	155	256	95	107
Nor. 5	83	81	61	74	134	90	91	140	192	103	125
Nor. 6	56	43	22	28	190	50	88	180	640	120	107
Nor. 7	16	27	14	16	200	34	81	123	770	140	116
Mean	51	57	48	53	134	62	89	149	370	112	111

* Epi. 1–9 received epinephrine infusion and Nor. 1–7 received norepinephrine infusion.

† See table 1 for key to abbreviations.

‡ Tubular maximum for glucose = GFR $\times$ Art. Conc. $-$ UV

little scatter, and the mean lies just slightly above the true median (fig. 1). At the point where renal function is markedly depressed, the tubular maximum for glucose, renal plasma flow, and glomerular filtration rate appear to have decreased to about the same degree (table 2).

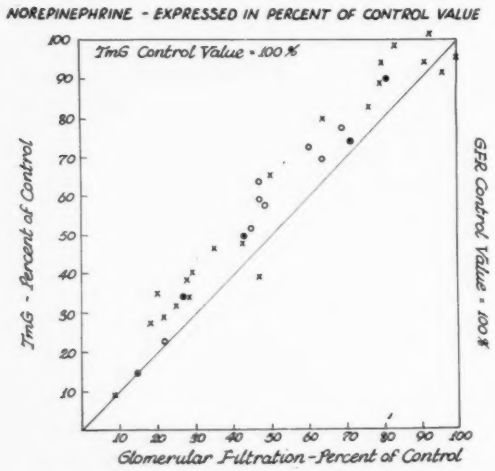

FIG. 1. Relationship of glomerular filtration rate to maximum tubular reabsorption of glucose, expressed in per cent of control value. ○, GFR is plotted against Tm_g after epinephrine infusion, same study periods as recorded in table 2. ●, GFR is plotted against Tm_g after norepinephrine infusion, same study periods as recorded in table 2. ×, GFR is plotted against Tm_g after epinephrine and norepinephrine. These study periods are from the same experiments but represent study periods during varying rates of infusion not included in table 2.

In order to evaluate the effect of adrenergic blockade, imidazoline hydrochloride (Regitine)* was administered to seven dogs, following which norepinephrine was administered to two and epinephrine to five. Infusion rates were those which had previously caused a decrease in renal plasma flow to 70 per cent or less of the control values. After the blockade, the infusion of norepinephrine had no significant effect on blood pressure or renal function. However, epinephrine resulted in a marked drop in blood pressure (epinephrine reversal). The drop was so marked in two of the five dogs that accurate renal function studies were not possible due to the decreased filtration pressure and resultant oliguria. The vasodilatory effect on the other three dogs was not as marked. One of these showed essentially no change, but the other two experiments were quite instructive and the results are consequently recorded in table 3. In these the renal plasma flow did not change significantly but the glomerular filtration rate decreased about 50 per cent, most likely a reflection of low hydrostatic pressure within the glomeruli. Both dogs showed a clear-cut reduction in functioning tubular mass when

* Supplied through the courtesy of Dr. Jock L. Graeme, Ciba Pharmaceutical Products, Inc.

TABLE 3.—*Response of Renal Hemodynamics to Epinephrine before and after Adrenergic Blockade*

Dog No.	UV*	GFR*	RPF*	RBF*	FF*	Tm_g	GFR/Tm_g	MBP*	RVR*
	cc./min.	*cc./min.*	*cc./min.*	*cc./min.*		*mg./min.*		*mm. Hg*	
Epi. 1									
Cont.	.5	37	198	310	.19	147	.25	137	.44
Epi.	.4	17	91	157	.19	77	.22	185	1.18
Regetine†	1.1	43	220	380	.20	170	.25	95	.25
Epi.	1.1	18	213	370	.08	143	.13	75	.20
Epi. 5									
Cont.	.8	41	226	376	.18	120	.34	120	.32
Epi.	.4	26	115	205	.23	84	.31	155	.76
Regetine†	.6	38	230	410	.17	118	.32	110	.27
Epi.	.5	21	218	389	.10	104	.20	55	.14

* See table 1 for key to abbreviations.

† Two mg. per Kg. body weight.

In both dogs there was a parallel reduction in GFR and Tm_g after epinephrine alone due to a decrease in the number of active nephrons. After adrenergic blockade the vasoconstrictive response to epinephrine was replaced by vasodilatation with a drop in blood pressure. Although the GFR decreased, the Tm_g did not change since the number of active nephrons was unaltered and all tubules continued to transport glucose.

epinephrine was given alone. This did not occur when the epinephrine was preceded by sympathetic blockade (Regitine) despite the 50 per cent decrease in glomerular filtration rate.

Discussion

The observations in these experiments indicate that there is no essential difference in the response of the kidney to epinephrine and its possible precursor, norepinephrine, and that the first and most prominent effect is on the efferent arterioles, thus increasing the renal vascular resistance in this segment. As a result, the renal plasma flow initially decreases in the presence of a maintained glomerular filtration rate, and an increase in the filtration fraction. This has also been noted in man following the administration of epinephrine[6, 7] and phenylephrine (Neosynephrin).[8] In the present experiments, the maximum tubular reabsorption of glucose did not change significantly as long as the glomerular filtration rate was maintained despite a decrease in renal blood flow. This indicates no change in the number of tubules actively reabsorbing glucose from the glomerular filtrate.

As the infusion rate is increased and the vasoconstrictive effect on the kidney becomes more prominent, the glomerular filtration rate decreases (table 1 and 2) in proportion to the decrease in renal plasma flow. In a few animals this proportionate decrease in glomerular filtration rate and renal plasma flow occurs initially without the primary decrease in renal plasma flow alone and its resultant increase in filtration fraction. Regardless of whether this proportionate decrease in renal plasma flow and glomerular filtration rate occurs initially or late, when it does occur it suggests that the afferent arterioles share in the increased vasoconstriction, and that a significant number of glomeruli may be eliminated from the renal circulation. This concept is supported most emphatically when one notes the relationship between glomerular filtration rate and maximum tubular reabsorption of glucose (tables 2 and 3 and fig. 1). At first the ratio GFR:Tm_g decreases slightly and then it remains constant while both the filtration rate and tubular maximum decrease to a parallel degree. One must conclude that a reduction in equal numbers of filtering glomeruli and tubules actively transporting glucose has taken place because the concept of measuring tubular maximum[12] is based on the fact that the blood level of glucose be maintained high enough to insure a concentration in the glomerular filtrate far in excess of the amount that the tubules are able to transport. The difference between the amount of glucose filtered and that lost in the urine represents the amount reabsorbed or transported by the tubules. Despite the fact that the glomerular filtrate might be reduced in some of the nephrons, there would remain adequate glucose to continue to measure maximum reabsorptive ability of these tubules. Under such circumstances, if the glomerular filtration rate is reduced but at the same time all the tubules continue to transport glucose at a maximum rate, then the ratio of filtration rate to tubular maximum must decrease. In the present study, the tubular maximum did not remain constant, as noted above, but rather the glomerular filtration rate and tubular maximum decreased together and their ratio remained constant, indicating a decrease in the number of active nephrons. The small but consistent decrease in the ratio because of the greater initial decrease in glomerular filtration rate does in fact indicate that some of the glomeruli are filtering at a reduced rate rather than being constricted out of the circulation. These concepts are further confirmed by table 3, showing the results of giving these animals epinephrine with the usual reduction in filtration rate and tubular maximum. However, when this was repeated following an adrenergic blocking agent, a generalized vasodilatation with a drop in blood pressure (epinephrine reversal) was noted. Apparently the kidney shared in this decrease in peripheral resistance, since the renal blood flow was not altered and the glomeruli were not eliminated from the renal circulation as they were before the blockade. However, due to a drop in systemic blood pressure, and consequently glomerular filtration pressure, the glomeruli now filtered at a reduced rate and the glomerular filtration rate decreased significantly. This resulted in a drop in the filtration fraction. At the same time,

nearly all tubules continued to reabsorb glucose. As a result, the GFR:Tm_g ratio decreased greatly (dogs Epi. 1 and Epi. 5, table 3). We can therefore conclude that epinephrine and norepinephrine are able to cause renal vasoconstriction to the extent that glomeruli are eliminated from the renal circulation, and that this effect can be blocked by adrenergic blocking agents. These observations are in direct contrast to the assumption that maximal tubular transport for glucose, Diodrast, and paraaminohippurate are independent of glomerular filtration rate, and that the only way that changes in tubular function can be produced is by glomerular and tubular damage or by inhibition of the transporting mechanisms.

Trueta and associates[16] recently aroused interest with their assertion that neurogenic and circulatory stress as well as vasopressor drugs activate renal subcortical arteriovenous shunts, thus bypassing the normal cortical glomeruli. Since direct blood flow studies[9] and renal clearance studies[10] following sciatic nerve stimulation and hemorrhage have failed to confirm these observations, it seemed worthwhile to analyze the data in the present study for evidence of vascular shunting following epinephrine and norepinephrine. If blood were shunted past the normal glomeruli and renal parenchyma to any significant extent, the ratios GFR:RPF and Tm_g:RPF would decrease. In addition, renal venous blood should show progressively increasing amounts of oxygen (arterialization) and the extraction of paraaminohippurate should decrease since most of this substance is extracted and secreted into the tubules as the blood circulates through the peritubular capillaries after it leaves the glomeruli.[12] None of these predicted alterations were observed. The filtration fraction (GFR:RPF) either increased or it did not change. A similar observation was made on the ratio of Tm_g:RPF (table 2). The renal venous blood did not become arterialized. The A-V oxygen difference at first did not change significantly, but as the renal blood flow became greatly reduced the oxygen content of renal venous blood progressively diminished. The extraction of paraaminohippurate showed considerable random variation (table 2), but it increased in as many animals as it decreased. This confirms a previous observation.[10] Only when the renal plasma flow decreased to about 10 per cent* of normal or below was the paraaminohippurate extraction affected consistently. Then it decreased. This may be due to the increasing importance of extraparenchymal blood flow, or may represent back diffusion of paraaminohippurate due to the low urine output.

Although more marked, the changes noted in the present studies are essentially similar to changes noted following sciatic nerve stimulation.[10, 11] In these latter experiments no attempt was made to determine whether the decrease in renal function associated with sciatic nerve stimulation was due to a neurogenic reflex vasoconstriction or due to the liberation of a circulating vasoconstrictive agent such as epinephrine. It may have been either or both. Certainly one might expect the liberation of epinephrine from the adrenal medulla following sensory nerve stimulation. Although the present study clearly demonstrates decreasing numbers of active glomeruli, dye injection studies[9] suggest that this is not limited to anatomic areas, but rather that the glomeruli have a graded threshold of response to vasoconstrictive substances. The peripheral cortical glomeruli seem to have a lower threshold and may show a decrease in blood flow before the deeper ones do, but this does not indicate any shunting mechanisms. It only means that the deeper glomeruli are left to carry on whatever renal function remains.

Conclusions

1. Epinephrine and norepinephrine, when administered by continuous infusion, caused a marked reduction in renal blood flow, renal plasma flow (RPF), glomerular filtration rate (GFR), and maximum tubular transport of glucose (Tm_g). There was no essential difference in the response to the two drugs.

2. In the majority of instances the renal plasma flow decreased and the filtration fraction increased before changes in other renal functions became evident, apparently due to efferent arteriolar vasoconstriction. As the in-

* Not accurate due to very low urine volumes at this stage of reduced renal function.

fusion rate was increased, there followed a proportional decrease in renal plasma flow, glomerular filtration rate, and maximum tubular absorption of glucose. The GFR:Tm_g ratio remained constant in the face of a decrease in the absolute values of both filtration rate and tubular maximum. These changes in renal hemodynamics are probably due to a decrease in the number of active nephrons.

3. Under the conditions of the experiment and similar conditions of stress, there seems to be sufficient evidence to conclude that active nephrons in large numbers can be completely occluded from the renal circulation in dogs and that this response can be prevented by adrenergic blockade. However, there is not sufficient evidence to conclude that the sympathetic nervous system regulates the renal circulation under normal conditions or that glomeruli "wink in and out of the renal circulation" as noted by Richards and Schmidt in amphibians.

4. There is no evidence from this study to support the hypothesis that epinephrine or norepinephrine activate renal vascular shunts in dogs.

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CLINICAL PROGRESS

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Atherosclerosis. A Symposium

GUEST EDITOR: EDGAR V. ALLEN, M.D.

PARTICIPANTS: LOUIS N. KATZ, M.D., ANCEL KEYS, M.D., AND JOHN W. GOFMAN, M.D., PH.D.

Introduction

By EDGAR V. ALLEN, M.D.

THIS symposium is the result of participation by Doctors Katz, Keys, and Gofman in a discussion of various aspects of atherosclerosis which was a part of a postgraduate course in Peripheral Vascular Diseases, conducted under the auspices of the American College of Physicians, by the Staff of the Mayo Clinic, the Faculty of the University of Minnesota (Mayo Foundation for Medical Education and Research), and invited speakers, at Rochester, Minnesota, in the fall of 1950.

The material presented at that time was so important and so timely that failure to record it in the medical literature would be, obviously, an error of great magnitude. With the consent of Dr. Herrman L. Blumgart, I asked that these manuscripts be prepared for publication in CIRCULATION. I need not emphasize here the importance of atherosclerosis, except to say that it is the most important disease in America and in areas where economics, diet and ways of life are similar to ours. It is my belief that this symposium constitutes the most important published work on atherosclerosis in medical history. For the clinicians, who must interpret advances in the laboratories for the benefit of their patients, I have requested that Doctor Katz, Doctor Keys and Doctor Gofman answer three specific questions:

QUESTIONS

1. *Has It Been Proved That Human Atherosclerosis Results from the Ingestion of Cholesterol and/or Fat?*

2. *In the Light of Present Knowledge, Is It Probable That Human Atherosclerosis Is Caused by the Ingestion of Cholesterol and/or Fat?*

3. *Would You Recommend That a Patient Who Has Clinical Evidence of Atherosclerosis Have His Diet Sharply Restricted in Cholesterol and Fat?*

ANSWERS

Louis N. Katz, M.D.

1. I would say the answer is yes. This is not to be taken, however, to mean that there is no other way of producing atherosclerosis. What I mean to imply is that endogenous disturbances in the metabolism of cholesterol and/or fat play a considerable role in the development of human atherosclerosis, but without the presence of cholesterol in the diet, this endogenous disturbance may not occur. It is my opinion that cholesterol is the offending agent in atherosclerosis.

2. The answer is yes, since I have already said yes with some minor amendments to the first question.

3. My answer is no. There is no reason in our present state of knowledge to have the patient sharply restricted on cholesterol and fat as a preventative or as a cure, *except:*

(a) When a person is overweight he should have his diet reduced so as to approach the ideal weight. There is no doubt that obesity is definitely associated with an increased frequency of atherosclerosis. However, it would appear that the obesity itself is not the cause; it is the fact that the American and European

diet is so rich in cholesterol that leads to the atherosclerosis tendency. Furthermore, in reducing, great care should be taken that there is no surplus of fat or cholesterol in the diet, since our work on chickens has shown that under such restricted diets the presence of any excess cholesterol is potentially more hazardous in developing atherosclerosis than on a normal caloric intake.

(b) When a patient has had two or more attacks of coronary insufficiency and/or myocardial infarction attributable to coronary atherosclerosis, and if that patient has a xanthomatotic tendency as revealed by the finding of his cholesterol level in the upper limits of normal, or above, then I believe I would recommend the reduction of cholesterol and fat in the diet. Otherwise, I would not, because I am a firm believer in the view that prohibitions should not be carelessly advocated until such time as it is clearly revealed that the prohibition has a great chance of being beneficial to the patient.

Ancel Keys, Ph.D.

1. The answer is a plain and simple *no*. The question would be more reasonably phrased to read: Has it been proved that human atherosclerosis *may* result—or results in some cases—from the ingestion of cholesterol and/or fat? But the answer would still be *no*.

2. The question must be more clearly defined. I think it more useful to try to answer several questions which, together, may cover the actual area of inquiry.

(a) If mankind stopped eating eggs, dairy products, meats and all visible fats, is it probable that all atherosclerosis would disappear? The answer is *no*, but I believe atherosclerosis would become very rare.

(b) Is it probable that the development of human atherosclerosis is affected by the amount of cholesterol in any ordinary diets? The answer is *no* except, possibly, in some rare individuals.

(c) Is it probable that the development of human atherosclerosis is affected by the amount of fats in any ordinary diets? The answer is *yes*, but there are probably large differences among individuals.

3. The answer is that I would recommend a sharp reduction in all dietary fats without paying any special attention to the cholesterol content of the diet. I would allow the use of an ordinary amount of eggs and milk in cooking, the use of skim milk for cereals and as a beverage, a good daily serving of *lean* meat or fish, and a boiled or poached whole egg for Sunday; but no butter, cream, oleomargarine, salad oil, mayonnaise, fried foods, gravy, ice cream, chocolate, or pastries made with shortening. Periodic measurements of serum cholesterol may help to judge the severity with which such restrictions should be maintained.

John W. Gofman, M.D., Ph.D.

1. Atherosclerosis is associated, and very likely in an etiologic fashion, with the presence of certain special lipoprotein classes in the blood. There appears to be a metabolic derangement of lipid metabolism which leads to the appearance of higher levels of such lipoproteins in the blood of some individuals when compared with others. In the human, both sexes show low levels of such lipoproteins in childhood and early adulthood. In the late twenties the male surges ahead of the female and remains ahead statistically until approximately the age of 55. This metabolic derangement in lipid metabolism we regard as the underlying defect in the evolution of atherosclerosis. It may well be, from evidence reported elsewhere,* that a deficiency of heparin or a heparin-like substance is at the root of this lipoprotein metabolic defect. Dietary fat can raise the serum level of the atherogenic lipoproteins of the S_f 35–100 class acutely in many humans, and variably from individual to individual, depending upon the lipoprotein metabolism. The restriction of fats and cholesterol can depress the level of the atherogenic lipoproteins of the S_f 12–20 class and also of lipoproteins the S_f 20–35 and S_f 35–100 classes. Yet there are individuals who can tolerate large quantities of dietary fat and cholesterol without showing abnormal lipoprotein patterns and, conversely, there are certain individuals who still show abnormal lipoprotein patterns in spite of dietary restriction of fat and choles-

* Page 134, reference 6.

terol. Thus we would consider that the ingestion of fats and cholesterol, while most likely not responsible for the lipoprotein metabolic error and hence not the basic cause of atherosclerosis, can definitely contribute to atherosclerosis in many individuals because of the susceptibility of such individuals to the alteration of lipoprotein levels through diet.

2. This question has been partially answered in the answer to question one. We would reiterate here that, while the lipoprotein derangement which leads to atherosclerosis is probably not caused by dietary factors, it is exceedingly probable that dietary fat and cholesterol by unfavorably influencing the serum lipoprotein levels do contribute to the progression of atherosclerosis in a large fraction of the human population.

3. The vast majority of patients with clinical evidence of atherosclerosis will show elevations of the S_f 12–20, S_f 20–35, S_f 35–100 classes of lipoproteins. A large proportion of such patients will show improvement in the lipoprotein pattern on dietary restriction of fats and cholesterol, which improvement our evidence already indicates will lessen further clinical manifestations of atherosclerosis. Therefore, the restriction of fat and cholesterol in the diet of such a patient has a very important place in the prophylactic and therapeutic armamentarium. It should be kept in mind, however, that because of the variability in ease of influencing lipoprotein levels by dietary measures certain patients will respond more favorably than others. We know at present of no way of predicting in a given patient whether or not the response to diet in the form of lipoprotein lowering will be large, intermediate or trivial. If a patient's lipoprotein levels can be studied ultracentrifugally, and it can be demonstrated that he responds to dietary restriction of fats and cholesterol with a significant lowering of lipoprotein levels, we would feel that there is ample reason to expect that atherogenesis can, in part at least, be suppressed by dietary means.

Experimental Atherosclerosis

By Louis N. Katz, M.D.

THIS presentation is concerned exclusively with one variety of arteriosclerosis, atherosclerosis. This subject delineation is not an arbitrary or artificial one. The term *arteriosclerosis* is a generic one. It refers to several distinct pathologic entities producing thickening of the vessel wall, embracing such entities as atherosclerosis, Mönckeberg's sclerosis, arteriolosclerosis, and hyperplastic arteriosclerosis. Awareness of this fact is absolutely essential for progress in this field. Recent research reinforces the conclusion that these are different entities. The attention of investigators is correctly focused today on the problem of the etiology and pathogenesis of *atherosclerosis*, since this is the lesion among the arterioscleroses which is overwhelmingly responsible for morbidity and mortality in man.

Until very recently atherosclerosis was a step-child problem of medical research commanding very limited resources of personnel, equipment, plant and money. This situation, only partially improved upon at present, is a consequence of several circumstances. Among them, one of the most important is a fundamentally erroneous concept developed in the medical profession itself—the senescence "theory" of the genesis of the arterioscleroses. This "theory" maintains that the arterioscleroses are inevitable results of physiologic aging processes. This "theory" likewise regards the specific entity atherosclerosis as such an unavoidable process of aging. The stagnating influence of this "theory" upon medical research has been overwhelming. It engendered an atmosphere of helplessness and hopelessness that was for many years a serious brake on all investigation.

This "theory" is a patently erroneous dogma. Certainly today overwhelming clinical evidence exists that atherosclerosis occurs in some very young people and is absent in some very old people. This indisputable evidence is alone sufficient to demonstrate that atherosclerosis cannot be an inevitable by-product of senescence. Rather, senescence and atherogenesis are two distinct and not necessarily related processes. Data from the experimental laboratory reinforce these conclusions of clinical research. Moreover, these data supply considerable support for the concept that atherogenesis is consequent upon an alteration in lipid metabolism, particularly in cholesterol metabolism.

It is upon the basis of this *cholesterol concept of atherogenesis* that fruitful research in this field is proceeding apace in a number of laboratories. The basic tenet of this concept may be simply stated: without an altered lipid-cholesterol metabolism little or no atherosclerosis will develop regardless of any other alterations in the arterial wall, including senescent changes. Obviously, if atherosclerotic lesions are the result—or even only in part the result—of altered lipid-cholesterol metabolism, then they are not inevitable. The whole foundation of the senescence theory is rendered untenable. The possibility, nay inevitability, presents itself that preventing or reversing the altered lipid-cholesterol metabolism will eliminate atherosclerosis. Thus, a hopeless situation is changed to one full of promise. Research in this field, by attacking the problem of the detailed interrelations

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between altered lipid-cholesterol metabolism and atherogenesis, can look forward to forging the scientific preconditions for eliminating atherosclerosis as a disease.

Evidence from Man

The cholesterol concept of atherosclerosis, the basis of almost all experimental work in this field at the present time, has an extensive foundation in clinical research. At least four sources have furnished supporting evidence for it: histopathology, biochemical pathology, ethnopathology and clinical pathology. A review of the extensive data from these sources is beyond the scope of this presentation. To summarize briefly the essential facts from these sources, histo- and chemicopathology early revealed that extensive lipid and cholesterol deposition is a hallmark of the atherosclerotic lesion. From the ethnopathologic viewpoint, comparative studies of vascular lesions among different peoples, including Costa Ricans, Okinawans, Chinese, Japanese, American and African Negroes, Eskimos and others, indicate that significant differences exist among peoples in incidence and severity of atherosclerosis. These differences appear to stem from culturally conditioned variations in nutrition and diet, rather than from racial, climatic or other influences. Specifically, a high correlation is frequently demonstrable between presence or absence of atherosclerosis and luxus or paucity of foods high in animal fat and cholesterol. Data accumulated in European countries during and after World Wars I and II lend further weight to the concept that there is a relationship of diet to atherogenesis. From these multiple studies the following tentative conservative conclusion appears justified: atherosclerosis is generally more frequent and severe in well nourished, particularly overnourished, people subsisting on diets rich in animal fat. Finally, from the clinicopathologic viewpoint, it is abundantly clear that in a number of disease states characterized by alterations in cholesterol metabolism and a prolonged hypercholesteremic phase, among them hypothyroidism, the nephrotic syndrome, essential familial xanthomatosis, biliary obstruction, and diabetes mellitus, premature severe atherosclerosis is inordinately frequent. Moreover, evidence has recently accumulated indicating that patients with coronary atherosclerosis without gross hypercholesterolemia have subtle alterations in cholesterol metabolism and a "xanthomatous tendency." The suggestion, based on these data, of a close association between alterations in cholesterol metabolism and atherogenesis is further reinforced by the recent work of Gofman and his colleagues demonstrating abnormalities in circulating cholesterol-bearing lipoproteins in association with clinical atherosclerosis. This, in brief, constitutes the clinicopathologic background and foundation for experimental atherosclerosis.

Experimental Atherosclerosis

History

Experimental atherosclerosis was first successfully induced in animals in the period 1908 to 1912. Prior to that time, all experimental attempts to reproduce the atherosclerotic lesion of man had failed, although arterial lesions had been produced by a number of procedures in animals (such as treatment with drugs, pathogenic bacteria, toxins). However, the resultant changes in the vessels resembled the Mönckeberg type of human arteriosclerosis (medial calcinosis, senile arteriosclerosis), rather than atherosclerosis. In 1908 a group of investigators working in St. Petersburg studied the effects of various dietary regimens on vascular pathology. They observed that rabbits fed diets containing meat, milk or eggs developed atherosclerosis. It was soon demonstrated, particularly by Anitschkow, that the biochemical factor responsible for these lesions was cholesterol. Conclusive proof was advanced that this sterol was the atherogenic stimulus. Experimental atherosclerosis as a definitive field of research endeavor dates from these discoveries. It is noteworthy that to this day experimental atherosclerosis has not been successfully produced by any other means than cholesterol administration (except avian stilbestrol-induced atherosclerosis, a lesion secondary to endogenous endocrine-stimulated hypercholesteremic hyperlipemia).

The Chick as an Experimental Animal

About 10 years ago this department became interested in experimental atherosclerosis. Our studies were carried on in the past decade principally in the chick. Our choice of this experimental animal was not fortuitous. Rather, it was based on a purposeful attempt to proceed along lines obviating criticisms leveled by many at the use of the rabbit for such atherosclerosis research. The rabbit is a herbivorous species not normally ingesting cholesterol. Moreover, on its usual diet it does not naturally develop vascular lesions of the atherosclerotic variety. Finally, until the last decade experimentalists had experienced only limited and indifferent success in attempts to induce gross atherosclerotic lesions by cholesterol feeding in species other than the rabbit. All these facts led many workers to question seriously the relevance of cholesterol-induced atherosclerosis in the rabbit for an understanding of the pathogenesis of the human disease. It was upon this basis that we sought to find a more suitable experimental animal. The chick was finally selected after a careful survey of the extant literature.

The chick, like man, is omnivorous, and develops atherosclerotic lesions of the great vessels spontaneously. In early studies it was quickly demonstrated that cholesterol feeding led to hypercholesteremia and eventually to atherogenesis in chicks. Such cholesterol-fed birds had gross atherosclerosis not only of the aorta, but also of the major systemic vessels, including the coronary arteries. These cholesterol-induced lesions were readily distinguishable from spontaneous lesions. Further, cholesterol was readily shown to be the decisive atherogenic stimulus in chicks, as in rabbits.

These initial studies demonstrated that the chick is of unique utility in offering two types of lesions for experimental study, the spontaneous and the cholesterol-induced. In 1946 the horizon and methodology of experimental atherosclerosis in the chick were further broadened. In that year Chaikoff and his associates showed that atherosclerosis occurred in cockerels having a prolonged endogenous hyperlipemia induced by implantation of estrogenic material. Horlick and Katz confirmed this finding and extended it by demonstrating that the lesions in stilbestrol-treated chicks were definitely not of the spontaneous type. Thus, a third experimental lesion in chicks became available for study. This avian species possesses, then, a unique versatility which further enhances its utility in atherosclerosis research.

Morphology of Atherosclerosis in the Chick

In several publications from this department, a detailed description has been given of the morphology of spontaneous, cholesterol-induced and stilbestrol-induced atherosclerosis in cockerels. A general review of the pathology of these lesions is beyond the scope of this presentation. However, several specific points may be noted: (1) Detailed microscopic studies indicate that throughout the arterial tree of stilbestrol-treated or cholesterol-fed chicks the primary lesion of experimental atherosclerosis is the foam cell intimal cushion. This lesion, so-called pure atheroma, is almost certainly the first stage of atherogenesis. The morphologic patterns of more advanced lesions are apparently the result of evolutionary pathologic processes secondary to atheroma. (2) It is possible by prolonged cholesterol feeding to induce in chicks the spectrum of atherosclerotic changes seen in human lesions including foam cell plaques, necrosis and atheromatous abscesses, fibrosis and hyalinization, calcification and cartilaginous-osseous metaplasia. Ulceration of atherosclerotic plaques with thrombus formation is the only lesion seen in man that has not been observed in cholesterol-fed chicks. (3) Cholesterol feeding apparently aggravates and intensifies spontaneous lesions. It would appear that the fibrotic spontaneous lesion is a site of predilection for cholesterol and lipid deposition, with subsequent evolutionary atherosclerotic changes. (4) Despite persistent dogma to the contrary, our experiments conclusively demonstrate that atherosclerotic lesions are reversible. (These findings are in accord with accumulated observations in man and rabbit.) Horlick and Katz demonstrated in the cholesterol-fed chick that in the weeks following cessation of cholesterol feeding, definite regression and

healing of cholesterol-induced lesions occurred. Previously existing moderately severe atheromatous lesions apparently completely healed and disappeared. More advanced lesions underwent partial resolution and evolution.

The question has been repeatedly posed: are experimental and human lesions morphologically similar? Even the most severe critics of the cholesterol concept of atherosclerosis cannot fail to note the conspicuous similarities between cholesterol-induced lesions—whether in rabbit, dog or chick—and the lesions seen in man. Taking into consideration the anatomic differences among the various species in architecture of the great vessels, the similarities between experimental cholesterol-induced and human lesions are indeed remarkable. That this resemblance is more than fortuitous is further emphasized by the fact that such lesions have not been produced experimentally by any other means.

Amount and Duration of Cholesterol Feeding

Our initial experiments on chick atherosclerosis placed us in a position to study possible exogenous and endogenous factors influencing the three types of avian lesions. However, preliminary to such investigations it became essential to quantitate the relation of the amount and duration of cholesterol feeding to the degree of hypercholesterolemia and to the incidence and severity of atherosclerosis. Toward this end several experiments were accomplished utilizing various levels of cholesterol in the diet and various feeding periods. Further, in order to permit quantitative evaluation of lesions, a system for gross grading of aortas for atherosclerosis was devised. This grading method, like others, is undoubtedly empiric and subjective. However, when employed with necessary precautions to guarantee treating all specimens as unknowns, it yields reliable information as to both incidence and severity of lesions. Hence it makes possible quantitation of pathologic data. By means of this grading method a general relationship is readily demonstrable between atherogenesis (incidence and severity of lesions) and cholesterol ingestion (amount and duration of sterol feeding). Thus with ranges of dietary cholesterol between 0.25 and 2.0 per cent (plus 5 per cent cottonseed oil), biochemical and pathologic alterations are quantitatively parallel. This is true both with chicks placed on experimental diets at 4 to 6 weeks of age and when 1 day old. In the course of these studies an additional basic methodologic principle became clear: In order to assess accurately the influence of various factors on experimental atherosclerosis, studies must be controlled with respect to each and every one of the following factors—age, sex, initial weight, feed intake, final weight and (at least in the chick) season. Attention to these elements in experiments on atherosclerosis insures a high degree of reliable quantitation in results.

Undernutrition and Overnutrition

Based on these studies it became possible to determine the influence of various factors on experimental atherosclerosis. The influence of one such factor, undernutrition, was explored in several experiments. In an early experiment, Dauber and Katz demonstrated that underfeeding per se (without cholesterol supplement in the diet) failed to induce lesions of the cholesterol type or to influence spontaneous atherogenesis. Subsequently, Rodbard and co-workers analyzed the effects of undernutrition on cholesterol-induced lesions. In one series of experiments chicks were fed mash containing either 0.25 per cent cholesterol plus 5 per cent oil or 2 per cent cholesterol. At each dietary level, one group of birds was permitted to eat ad libitum, another was given only 60 to 70 per cent as much mash. Chicks on this reduced dietary intake received less cholesterol than the controls given the same mash ad libitum. Nevertheless the semistarved birds tended to have a more severe hypercholesteremia than the controls. At the conclusion of the experiment incidence and severity of atherosclerosis in the undernourished cockerels were as great as or greater than in the control birds on an unrestricted diet of similar composition. Apparently the underfed birds were not readily able either to draw upon the elevated plasma lipids as a source of calories or to dispose of the exogenous cholesterol

load. Thus it may be concluded that cholesterol remains an atherogenic stimulus regardless of the level of over-all caloric intake. It may be further suggested that in Europeans and Americans, where a definitive correlation has been shown between obesity and intensified atherogenesis, this influence of obesity may be attributable to the associated increased intake of specific atherogenic material, that is, cholesterol.

In another series of experiments, Rodbard and co-workers approached the same general problem somewhat differently; chicks were fed cholesterol diets during repeated short intervals. During interim periods (one to five days in duration), they were either starved or fed plain mash. A third group subsisted on the cholesterol diet continuously. The cholesterol-fed birds, starved during alternate periods, developed marked hypercholesteremia and atherosclerosis, resembling the findings in cockerels on a continuous cholesterol mash diet. In contrast, chicks alternating between cholesterol diet and regular mash exhibited only slight hypercholesteremia and atherosclerosis. Thus intermittent periods of starvation apparently hindered, rather than facilitated, the disposal of exogenous cholesterol load, whereas intermittent periods of regular mash facilitated such disposal. Over-all adequate intake of a balanced diet apparently made a key contribution to preventing dietary induced hypercholesteremia and atherosclerosis. Whether this effect is mediated by dietary or endocrine factors, or both, remains to be elucidated. These findings suggest the possibility that in man the effects of exogenous cholesterol on cholesteremia and atherogenesis may be at least in part regulated by over-all nutritional status.

In contrast to these experimental studies on semistarvation, only limited observations are available on the effects of overfeeding on experimental atherogenesis. To our knowledge only one report in the literature deals with this problem. Wolffe and associates indicate that force fed geese exhibit an increased incidence of both spontaneous and cholesterol-induced atherosclerosis. Evaluation of these findings awaits publication of the complete data. Since obesity, the level of food intake in general, and cholesterol intake in particular have all been implicated as important factors in human atherogenesis, further experimental studies are indicated on excessive dietary intake and atherosclerosis.

Neutral Fat in Diet

Among other exogenous factors possibly influencing atherogenesis, neutral fat intake has been studied experimentally by us. In initial experiments, Dauber and Katz observed no effect of 20 per cent cottonseed oil diets on lipemia or spontaneous atherogenesis in chicks. More recently Stamler and co-workers extended these observations to chicks fed mash supplemented with 5 per cent cottonseed oil. Here again normal plasma lipid patterns were observed, no effect on spontaneous atherogenesis was noted, and no lesions of the cholesterol-induced variety supervened.

These experiments cannot be interpreted as indicating that neutral fat ingestion is not a factor in human atherogenesis. Clinically, neutral fat and cholesterol ingestion are almost invariably combined—in contrast to the foregoing experiments. Considerable evidence exists that under such circumstances triglyceride influences cholesterol metabolism. Moreover, a recent experiment in our laboratory also indicates that under certain circumstances neutral fat ingestion affects cholesterol metabolism and atherogenesis in the chick. Briefly, Stamler and associates demonstrated that depancreatized chicks respond differently to cholesterol feeding, depending on the presence or absence of cottonseed oil in the mash.

Cholesterol-Free and Fat-Poor Diet

In other studies on exogenous factors, Horlick and his colleagues analyzed the effects of a specially prepared defatted mash on both spontaneous and stilbestrol-induced atherosclerosis in cockerels. They also investigated the influence of such a low fat, cholesterol-free mash on regression of cholesterol-induced atherosclerosis occurring upon cessation of cholesterol feeding. In the first study, chicks receiving defatted mash developed spontaneous aorta lesions later than birds subsisting

on regular mash; these lesions were less extensive and severe. However, lesions were present. Hence the defatted mash diet failed to eliminate spontaneous arteriosclerosis in the chicks although it may have retarded this pathologic process. Apparently an exogenous source of lipid and cholesterol is not essential for spontaneous arteriosclerosis in the chick. If plasma lipids play a key role in such spontaneous arteriosclerosis, endogenous sources continue to make available sufficient lipids for this process. It might appear from these experiments that the spontaneous lesions produced are primarily arteriosclerotic and only secondarily atherosclerotic.

In a second experiment, Horlick and Katz observed that a defatted mash was without significant effect on the endogenous hyperlipemia and hypercholesteremia induced by stilbestrol implantation in cockerels. Stilbestrol-induced atherogenesis developed concommitant with the hypercholesteremia in these estrogen-treated birds fed a defatted mash.

In a third study with defatted mash, the influence of this diet on regression of cholesterol-induced lesions was analyzed by Horlick and Katz in chicks rendered atherosclerotic by a prolonged period of cholesterol feeding. The specially prepared defatted mash was no more valuable in effecting the regression of atherosclerotic lesion than the regular chick starter mash.

The fact that spontaneous arteriosclerotic lesions occur with cholesterol-free, fat-poor diet, and that this diet had no obvious effect in eliminating the endogenously induced lesions casts some doubt on the view that *low fat diets in man* exert any marked influence on atherosclerosis. The conclusive proof for such a view must still be forthcoming. It is not at present available. It seems pertinent to suggest that in the present state of knowledge, use of low fat, low cholesterol diets in man would appear justified only (a) in cases with abnormally high cholesterol blood levels and (b) in patients with more than one episode of recent myocardial infarction, who have blood cholesterol levels at the upper limits of normal or above normal. Furthermore, the dietary restriction under such circumstances must be drastic; for example, a diet of 25 to 50 Gm. of fat per day must be rigidly adhered to, and it must be persisted in for long periods of time. The obvious difficulties of pursuing such a program and the inconclusiveness of the results obtained should make one hesitant to undertake widespread use of such dietary restraints until the controversy concerning the effects is settled conclusively one way or the other.

Lipotropic Factors

Among dietary factors possibly influencing human and experimental atherosclerosis, greatest attention has focused on lipotropic factors. Until recently their value was not clear, since contradictory findings were reported concerning the effects of these factors. This confusion has been eliminated in the last year or two. Experiments in chick, dog and rabbit yielding negative results are particularly decisive in indicating that at least choline is of no value in the prophylaxis or therapy of atherosclerosis. In this laboratory Stamler and co-workers studied the possible prophylactic influences of choline and inositol in spontaneous, cholesterol-induced and stilbestrol-induced atherosclerosis in cockerels. In the studies of lipotropic factors in cholesterol-induced atherosclerosis, the effects of 1 per cent choline plus 1 per cent inositol were determined in birds fed three different concentrations of dietary cholesterol, 0.25, 0.5 and 2 per cent. In studies continuing from 15 to 35 weeks all experimental regimens were well tolerated; normal feed intakes and rates of weight gain were recorded throughout. All cholesterol diets produced hypercholesteremia and hyperlipemia of varying degrees, hypercholesteremia being the principle alteration in the plasma lipid pattern. Phospholipids rose, but disproportionately less than cholesterol so the plasma total cholesterol–lipid phosphorus (C/P) ratio increased significantly. At all levels of cholesterol feeding 1 per cent choline plus 1 per cent inositol failed consistently to lower hypercholesteremia and hyperlipemia. The lipotropic factors were without effect in ameliorating the minimal hypercholesteremia consequent upon feeding 0.25 per cent cholesterol mash. The data indicate that during the initial weeks of the experiment

addition of lipotropic factors to the diet actually aggravated hypercholesteremia. The exhibition of the phospholipid precursors choline and inositol failed significantly to elevate plasma phospholipid levels sufficiently or to correct the abnormally high plasma total cholesterol–lipid phosphorus ratios. Choline and inositol had only a limited incomplete lipotropic effect on cholesterol-induced hepatic lipidosis and completely failed to influence the lipidosis in other organs, including the aorta. Similarly the lipotropic factors failed to reduce the incidence or severity of cholesterol-induced lesions in either the thoracic or abdominal aorta.

In the companion experiments, Stamler and co-workers demonstrated that the lipotropic factors were also without significant effect on the hyperlipemia of stilbestrol administration and on either stilbestrol-induced or spontaneous atherogenesis. Recent reports of carefully controlled studies by Firstbrook and Davidson and associates similarly indicate that choline is ineffective as a prophylactic or therapeutic agent against cholesterol-induced atherosclerosis in rabbits and dogs. Insofar as studies in man are concerned, adequately controlled clinical data are lacking; the efficacy of lipotropic factors in the prophylaxis or therapy of human atherosclerosis has not been demonstrated. Hence we deem it necessary to emphasize that neither clinical nor experimental foundations are present to justify the widespread prescription of costly preparations of lipotropic factors for human atherosclerosis. Such procedure merits condemnation on both scientific and socioeconomic grounds.

Aluminum Hydroxide Gel

Since cholesterol undergoes an enterohepatic circulation, the possibility presents itself that the intestinal disposal of cholesterol might be enhanced, plasma cholesterol levels thereby lowered, and atherogenesis retarded. Rothbard and his colleagues have been carrying out experiments on this problem in our laboratory. Utilizing a specially prepared aluminum hydroxide gel, it has been possible to decrease hypercholesteremia and atherogenesis in cholesterol-fed cockerels. This problem is under further study in our laboratory at the present time.

Cholesterol–Phospholipid Ratio

A number of recent investigators have brought forward evidence from studies on man suggesting that the plasma cholesterol–phospholipid (C/P) ratio may be a key factor in atherogenesis. Since cholesterol-induced atherosclerosis in rabbit, chick and dog is uniformly associated with a disturbed lipid pattern characterized by hypercholesteremia, altered cholesterol–phospholipid ratios and chylomicronemia the question arises: is the hypercholesteremia per se or the altered cholesterol–phospholipid ratio the decisive factor in atherogenesis? Can atherogenesis occur without an elevated cholesterol–phospholipid ratio?

Several studies in our laboratory bear upon this problem of cholesterol–phospholipid ratios and atherogenesis. First, it is noteworthy that estrogen-treated chicks, unlike cholesterol-fed birds, exhibit a plasma lipid pattern characterized by hyperphospholipemia in excess of hypercholesteremia, with a resultant lowering of the plasma cholesterol–phospholipid ratio. Aortic atherosclerosis eventually supervenes in birds subjected to prolonged estrogen treatment. Under these experimental conditions a fall in the cholesterol–phospholipid ratio prevents neither plasma lactescence nor aortic atherosclerosis.

In another experiment Stamler and Katz attempted to correlate plasma biochemical data and postmortem pathologic findings in individual chicks fed 0.25 per cent cholesterol mash for 35 weeks, beginning at 5 weeks of age. Analysis of these data reveal a close correlation between the level of hypercholesteremia and aortic atherogenesis in individual birds. In contrast, there was no correlation between presence or absence of induced lesions in the aorta and degree of elevation of the plasma cholesterol–phospholipid ratio. Thus, this experiment demonstrated a lack of correlation between plasma cholesterol–phospholipid ratios and aortic atherogenesis, together with a positive correlation between plasma cholesterol levels and aortic lesions.

Although these experiments indicate that

cholesterol–phospholipid ratios are not decisive factors for aorta atherogenesis, recent studies by Pick and associates in our laboratory indicate that cholesterol–phospholipid ratios and *coronary* atherogenesis may be closely interrelated. Thus, estrogen exhibition to cholesterol-fed chicks results in suppression of coronary atherogenesis. Concomitantly, the ratios are depressed to or toward normal, despite persistent cholesterol-induced hypercholesterolemia.

This finding of prophylactic inhibition of coronary atherosclerosis by estrogens may be a significant lead concerning the mechanism of the well known sex differential in human susceptibility to coronary atherosclerosis. Further, since cholesterol-fed chicks are not protected against aorta atherosclerosis by estrogens, but are protected against coronary lesions, it would appear that atherogenesis proceeds according to different biologic laws in different vascular beds. Evidence is extant indicating a similar phenomenon in man. Hence, investigation of experimental atherosclerosis should not be confined to aorta lesions, lest significant findings in such important beds as the coronary and cerebral be entirely overlooked.

Thyroid

In addition to the foregoing studies, this department has carried on a number of experiments on the influences of various endogenous factors upon experimental atherogenesis. Among such factors studied to date, thyroid hormone has been found to be far and away the most effective agent influencing experimental atherogenesis. In an initial study in this laboratory, Dauber and associates demonstrated that desiccated thyroid significantly depressed the hypercholesteremia of birds given diets supplemented with 0.5 to 2.0 per cent cholesterol plus 20 per cent cottonseed oil. In accordance with these plasma lipid patterns thyroid hormone significantly decreased the incidence and severity of cholesterol-induced atherosclerosis. In a subsequent study, Stamler and co-workers extended these observations to stilbestrol-induced atherosclerosis in cockerels. Although desiccated thyroid only temporarily depressed the hyperlipemia of chronic stilbestrol administration, it was remarkably effective in reducing the incidence and severity of lesions in the aorta.

The mechanism or mechanisms of this effect of thyroid hormone on atherosclerosis remain obscure. Various hypotheses have been advanced by different investigators, among them that thyroid exerts its effect directly on cholesterol metabolism, reducing the hypercholesteremic stimulus to atherogenesis; that thyroid hormone affects the tissue accumulation of cholesterol; that thyroid hormone alters vascular permeability. Unfortunately, little is known concerning the mechanisms whereby thyroid affects lipid metabolism. Recent studies with radioactive tracers indicate that thyroid influences the hepatic degradation of the lipids, effecting lipid depletion.

In one of our studies Stamler and his colleagues undertook to determine whether the influence of thyroid hormone on lipids and atherosclerosis is a simple by-product of induced hypermetabolism. A comparison was made of the effect of desiccated thyroid and of the hypermetabolism-inducing drug dinitrophenol on plasma and tissue lipids and atherogenesis in cholesterol-fed chicks. Despite the similar hypermetabolism-inducing potential of thyroid and dinitrophenol, markedly different effects of the two substances were observed in these cholesterol-fed birds. Unlike the birds given thyroid hormone, the dinitrophenol-fed animals failed to exhibit a depression of either hypercholesteremia or atherogenesis. This experiment therefore suggests that the effects of thyroid hormone on lipid metabolism and atherogenesis cannot be attributed solely to any generalized nonspecific increase in energy exchange it induces. Rather than being nonspecific by-products of increased metabolic rate, these actions of thyroid on cholesterol metabolism would appear to be effected via specific metabolic reactions involving hormone and lipids—reactions whose pathways are today obscure.

Pancreas

In view of the increased incidence and severity of atherosclerosis in clinical diabetes, the role of the pancreas (as well as the other endocrine glands involved in the pathogenesis

of diabetes) in experimental atherosclerosis merits considerable attention. Until recently, experimental work on this aspect of atherosclerosis was very limited in scope. A few reports indicate that atherosclerotic lesions eventually develop in chronic diabetic dogs, particularly in completely depancreatized insulin-maintained animals subsisting on a diet of moderate to high fat content without supplementary raw pancreas or lipotropic factor. Experimental work on these problems in the rat, a species which to date has proved to be particularly resistant to cholesterol-induced atherosclerosis, has been even more limited. In this and other departments no success has been obtained in efforts to induce atherosclerosis by cholesterol feeding in alloxan diabetic rats. In rabbits, several workers report cataracts, but no atherosclerosis, following long-standing alloxan diabetes. When alloxan diabetes is combined with cholesterol feeding, the unexpected observation was made that atherogenesis tended to be retarded. Duff and Paine attributed this finding to the interrelations between cholesterol and phospholipid (normal C/P ratios) in such animals. It has also been suggested that this inhibitory phenomenon may be due to undernutrition and emaciation in alloxan diabetic rabbits.

It may be noted at this point that the study of the role of lipotropic factors in experimental atherosclerosis has its roots in the original observations that totally depancreatized, insulin-treated dogs can be chronically maintained only if fed a supplement of raw pancreas or its decisive lipotropic factors, lecithin or choline. Hence, in a certain sense the studies on lipotropic factors (which, as already noted, have yielded negative results) are an aspect of the problem of the role of the pancreas in experimental atherosclerosis.

In our laboratory, we have studied this over-all problem in chicks. This animal is readily amenable to total pancreatectomy or alloxanization. In an initial study, Stamler and co-workers determined the effect of pancreatectomy on plasma and tissue lipids and on the three types of chick atherosclerosis. In totally depancreatized cockerels fed a regular mash, free of cholesterol or other supplements, both plasma lipid and carbohydrate level are within normal limits. These birds exhibit no overt signs of metabolic disturbance. Lesions of the induced variety do not develop, although these chicks exhibit a tendency to intensified spontaneous arteriosclerosis. Stilbestrol-treated, depancreatized birds also exhibit a plasma lipid pattern essentially similar to that of their unoperated controls.

When a supplement of cholesterol and cottonseed oil is added to the mash of depancreatized cockerels, a plasma lipid pattern emerges that is significantly different quantitatively from that of their paired controls. They consistently exhibit a far more severe hypercholesteremia; this is accompanied by intensified atherogenesis. In contrast, when depancreatized chicks are fed a mash containing cholesterol, but devoid of a cottonseed oil supplement, they exhibit a plasma lipid pattern essentially similar to their unoperated paired controls on a similar diet. Thus, the addition of neutral fat to the diet apparently plays a decisive role in the development of an inordinate hypercholesteremia in pancreatectomized cholesterol-fed chicks. Since depancreatized cockerels fed a cholesterol–cottonseed oil mash exhibit a response different from their paired controls, it may be concluded that this dietary regimen has brought out subtle defects of lipid metabolism in these birds. Similarly, it is possible to bring out subtle defects in carbohydrate metabolism. Although chronically depancreatized chicks on regular diet exhibit gross derangement in neither plasma lipid nor glucose level, the administration of adrenocortical extract to such birds results in a marked hyperglycemia, far in excess of that seen in unoperated controls, and reaching levels well into the severe diabetic range.

These two experiments indicate that in the chick, as in man, the pancreas apparently plays an important role in the metabolism of both the lipids and carbohydrates. This biologic similarity emerges despite initial data indicating that pancreatic deficiency has different effects on metabolism in chick and man. Our findings suggest that these apparent differences between man and chick are not necessarily

qualitative ones, but rather at least in part quantitative. The relationships of both lipid and carbohydrate metabolic effects to atherogenesis in the chick are under further investigation in this laboratory.

Hypertension

In view of the frequent clinical observation that hypertension is associated with intensified atherogenesis in man, we undertook to study the interrelationship between these two pathologic processes in the experimental animal. The demonstration by Lenel and associates in our laboratory that salt feeding induces a significant chronic rise in blood pressure in chicks made it possible to carry on such experiments. In an initial study, Stamler and Katz compared atherogenesis in salt hypertensive and normotensive cockerels subsisting on a diet of regular mash *without* a cholesterol supplement. The experimental regimens had no effect on plasma cholesterol concentration. Despite a significant elevation of blood pressure in the salt-treated animals, no gross lesions of the induced type were observed, nor was there any clear-cut intensification of spontaneous lesions. Thus, salt hypertension had little or no effect in grossly intensifying *spontaneous* arteriosclerosis in cockerels.

In a subsequent study, Stamler and coworkers analyzed the effect of another type of hypertension on atherogenesis in chicks subsisting on plain mash: namely, desoxycorticosterone acetate (DCA)–salt hypertension. Here again, in the absence of a supplement of cholesterol in the diet, no lesions of the induced type were observed, nor was there intensification of *spontaneous* lesions. It would appear that in the presence of consistent normocholesteremia, hypertension is ineffective as an atherogenic stimulus, both with respect to causing the appearance of induced lesions and with respect to intensifying spontaneous lesions. This finding is in accord with observations in this and other laboratories with several other species, including rabbit, dog, sheep and goat.

In contrast to such negative results, desoxycorticosterone-salt hypertension did intensify cholesterol-induced atherogenesis in cholesterol-fed cockerels. This observation, too, is consistent with the findings of other workers utilizing rabbits and dogs; namely, that hypertension intensifies atherogenesis when accompanied by a cholesterol diet. The mechanism of this effect remains obscure. Regardless of mechanism, however, the facts available from these experiments support the view enunciated by several investigators: cholesterol is the decisive factor in the pathogenesis of atherosclerosis, whereas hypertension acts rather as an intensifying agent, exerting this effect when the lipid metabolic situation favors atherogenesis.

Vascular Damage

Some workers attribute the effect of hypertension on atherosclerosis to a vascular damage presumably caused by hyperpiesis. Fundamental to such a concept is the problem: is preexistent vascular damage a prerequisite for lipid deposition and atherogenesis? Numerous attempts were made to clarify this problem experimentally. A host of noxious agents were tested for atherogenic effect, including bacteria, toxins, drugs, hormones, mechanical and thermal trauma. Although various lesions were experimentally produced by these methods, atherosclerosis was never produced. Thus it would appear that in the absence of an essential lipid metabolic alteration, vascular damage, per se, is ineffective as an atherogenic stimulus. On the other hand, experimental and clinical data from a number of sources indicate that foci of vascular damage are sites of predilection for deposition of atherogenic material, provided the necessary lipid metabolic alteration is present.

Some of the experiments in our laboratory bear upon this problem. In a recent study by Rodbard and his colleagues, 1 day old cockerels were placed on a diet of chick starter mash supplemented with 2 per cent cholesterol plus 5 per cent cottonseed oil. Weekly sacrifice of birds on this regimen revealed gross cholesterol-induced lesions of the aorta in birds as young as 5 weeks of age. It is apparent that these chicks had juvenile arterial tissue. Their vascular wall had not yet been subject to necrobiotic senescent alterations. More-

over, during their brief 5 weeks in the laboratory there was no indication in these healthy birds of the operation of pathologic stimuli noxious to the vessel wall other than the hyperlipemia itself. The occurrence of significant gross atherosclerosis in these cockerels suggests, therefore, that atherogenesis may proceed solely on the basis of deranged lipid metabolism, provided this is severe enough in degree and duration. On the other hand, Schlichter and associates have shown in dogs that vascular damage to the outer third or half of the aorta produced by cauterization focally alters the arterial wall, so that the subjacent intima becomes a site of predilection for deposition of administered atherogenic material (cholesterol). These and supplementary data of a similar nature from other laboratories lead us to agree with Anitschkow's original concept, advanced many years ago, that cholesterol may be a *primary* atherogenic stimulus. We are also in accord with his further concept that vascular damage may play a role in the arterial deposition of lipids. These ideas, called the "combined theory" by Anitschkow, recognize that a number of different factors are involved in the pathogenesis of atherosclerosis; they also recognize the key role of the lipids in atherogenesis, whereby a severe enough derangement of lipid metabolism may result in atherogenesis in previously normal vessels; they further recognize that with less marked derangements in cholesterol metabolism, atherogenesis may still proceed, particularly in sites of predilection produced by previous vascular damage.

Pituitary and Adrenals

In connection with these concepts of the role of vascular damage in the pathogenesis of atherosclerosis, considerable attention has recently been focused upon the influence of the adrenal steroids, particularly since several workers have demonstrated vascular injury in animals chronically treated with desoxycorticosterone acetate and other corticoids. This problem assumes further importance in view of the fact that clinical endocrine disorders characterized by excessive secretion of adrenal steroids (e.g., Cushing's syndrome) are associated with intensified atherogenesis. Introduction into clinical therapeutics of adrenocorticotropic hormone (ACTH) and cortisone further highlights the need to investigate the possibility that steroids may be atherogenic, particularly since chronic treatment with cortisone may result in a significant rise in the plasma cholesterol concentration of man. Finally we should take note of the fact that the adrenal cortex plays an active part in sterol metabolism as is indicated by their high concentration of cholesterol, their ability readily to discharge cholesterol, to synthesize cholesterol, and to accumulate ingested cholesterol. We have already briefly referred to the results of our studies on atherogenesis in desoxycorticosterone acetate–salt treated birds. Although moderate hyperpiesis supervened, no effect was observed on spontaneous lesions. However, cholesterol-induced atherogenesis tended to be moderately intensified. A more recent experiment by Stamler and associates further demonstrated that cortisone intensified aorta and coronary atherogenesis in cholesterol-fed chicks, although this steroid did not alter blood pressure or plasma lipid levels. Obviously these are not exhaustive experiments on the pituitary-adrenocortical axis and atherogenesis. The possible influences of other glycocorticoids remain to be explored. Such studies are currently in progress in this laboratory. Also in need of further study are the complex interrelationships between the hypothalamic-pituitary-adrenocortical system and the other endocrines.

Aging

Among the endogenous factors possibly influencing atherogenesis, careful consideration must be given to the problem of age. A recent study by Rodbard and associates in our laboratory yielded significant findings concerning the influence of age on cholesteremia and atherogenesis. These workers recorded age-associated variations in level of cholesteremia in cockerels on a diet of constant cholesterol content. Thus, during the first seven weeks of life, birds on a diet containing 2 per cent cholesterol plus 5 per cent cottonseed oil exhibited a cholesteremia in the range of 200

to 500 mg. per 100 cc. At about the eighth week, this cholesteremia increased spontaneously to a level of 800 to 900 mg. per 100 cc., although no change was instituted in the experimental regimen. This new high level of cholesteremia tended to maintain itself during the next 12 weeks. At about the twentieth week of age, with the same diet continuing, there was a secondary fall of the plasma cholesterol level to about 300 to 500 mg. per 100 cc. In accord with these plasma lipid findings, atherogenesis during the first seven weeks of life was slight, whereas it proceeded rapidly after the eighth week. This experiment indicates that endogenous factors varying with age influence the response of chicks to a diet containing cholesterol. These endogenous factors, conditioned by and varying with age, influence both cholesterol metabolism and atherogenesis. Preliminary evidence suggests that hormonal factors may play a key role in this varying pattern of endogenous control of cholesterol metabolism.

Gonads

Among other endogenous factors possibly influencing atherogenesis, attention must be focused upon the role of the gonads, particularly in view of the conspicuous sex difference in the incidence of coronary disease in human beings. Experimental work on the gonads and atherogenesis has been limited. An extensive investigation of this problem is currently in progress in our laboratory. As already indicated, estrogens have been shown to inhibit coronary lesions in cholesterol-fed cockerels. A few reports are extant of experiments in the rabbit. These observations are patently incomplete and require supplementation by more extensive investigation.

Species Differences

Among the problems that emerge in the course of studying atherosclerosis experimentally, perhaps the most intriguing is the one of species differences in susceptibility to lesions. Man, the chick and the duck develop atherosclerosis "spontaneously." The dog and the rabbit rarely do. Experimentally it is easy to produce gross atherosclerosis in rabbits or chicks. It is more difficult in guinea pigs, hamsters and ducks. It is still more difficult in dogs. To date it has proved impossible consistently to produce gross atherosclerosis in rats. Why these species differences in atherogenesis? In our laboratory Schlichter has suggested that they may depend on species variability in the adequacy of the vasa vasorum of the large arteries. On the other hand, considerable evidence exists indicating that species differences in atherogenesis may depend on species variability in lipid metabolism. Studies by Horlick and co-workers in our department, utilizing the intravenous cholesterol tolerance technic, suggest that such variations exist. Thus the disappearance time of intravenously injected cholesterol is not the same in three species investigated to date. For proportional amounts of cholesterol the disappearance time in the rabbit is about 72 hours, in the chick 24 hours, in the rat 12 hours. Recent ultracentrifuge and isotope studies also demonstrate species differences in lipoprotein and cholesterol metabolism. Moreover there are well-known marked species differences in the cholesteremic response to orally ingested cholesterol. In general, ease of hypercholesteremia production and ease of atherosclerosis production parallel each other among the various species.

Finally, it is noteworthy that only in the rabbit and chick (and perhaps in man) can atherosclerosis be produced with but slight hypercholesteremia, resulting from chronic cholesterol ingestion by these experimental animals. Undoubtedly further research will clarify the reasons for the foregoing species differences in lipid metabolism and atherogenesis. Undoubtedly such advances will be fruitful contributions to the ultimate solution of the whole atherosclerosis problem.

Minimal Cholesteremia

In the foregoing sections, we have briefly reviewed the experimental work of our department on atherosclerosis. As indicated, in many of our experiments the dosage of choles-

terol utilized resulted in marked hypercholesteremia and organ lipidosis, as well as atherosclerosis. The criticism has been frequently advanced that lesions occurring under such circumstances are fundamentally different from those seen in most human beings (excepting those with gross xanthomatosis), since atherosclerosis frequently occurs in people with presumably normal or near normal plasma and tissue cholesterol concentrations. In view of this frequently advanced criticism, Stamler and associates undertook two long-term experiments to explore this problem further, particularly in an effort to produce cholesterol-induced atherosclerosis in the chick with minimal concomitant hypercholesteremia and organ lipidosis. It was found that a diet of 0.25 per cent cholesterol mash induces a minimal hypercholesteremia and organ lipidosis in chicks. Maintaining chicks on this diet for periods beyond 15 to 20 weeks had a profound effect on atherogenesis, in the presence of minimal changes in plasma and tissue lipid concentrations. A high incidence was found of moderately severe gross atherosclerosis of the cholesterol-induced type in the thoracic aorta. These experiments demonstrated clearly that significant cholesterol-induced atherogenesis proceeds in chicks fed a dietary level of sterol inducing little or no hypercholesteremia and organ lipidosis. These findings in the chick are in accord with previous experimental work in the rabbit. When they are evaluated in relation to the latest data on man, these observations assume particular significance. Thus, today a mass of data exists demonstrating that a "xanthomatous tendency" (minimal hypercholesteremia) prevails in many people who are victimized by atherosclerosis. Moreover, considerable evidence is available indicating that cholesterol "input loads" (the quantity of ingested cholesterol per unit time that the body must absorb, transport, metabolize, turn over and excrete) influences atherogenesis in man. This conclusion is reinforced by the recent studies of Gofman indicating that diet may vary the concentration of various classes and species of plasma cholesterol-bearing lipoprotein molecules including classes and species tentatively implicated in the pathogenesis of atherosclerosis.

Conclusion

In conclusion, we may reiterate that a basic proposition has been the foundation of the work of this department on experimental atherosclerosis. The essence of this proposition is that altered cholesterol metabolism plays a key role in human atherogenesis. The corollary of this proposition is that study of experimental cholesterol-induced atherosclerosis—of the exogenous and endogenous factors controlling it—would yield knowledge of fundamental significance for our understanding of human atherosclerosis.

For many years some investigators rejected these concepts because atherosclerosis had been produced experimentally only in rabbits. The consistent production of gross cholesterol-induced atherosclerosis in omnivorous chicks and dogs and other species now compels rejection of this criticism. For many years some investigators maintained that experimental and clinical atherosclerosis were fundamentally different, since hypercholesteremia was a prerequisite for the former, whereas the latter occurred in many normocholesteremic persons. The consistent production of gross cholesterol-induced atherosclerosis in chicks and rabbits with minimal hypercholesteremia, as well as the demonstration of a "xanthomatous tendency" in many persons with atherosclerosis, now compels rejection of this criticism. During the last decade, particularly, research in both clinical and experimental atherosclerosis has brought overwhelming support to the basic tenet of the cholesterol concept of atherosclerosis. What conclusion must be drawn from this? Certainly present knowledge does not permit us to state that the atherosclerosis problem is solved. Certainly much basic clinical and laboratory research on both exogenous and endogenous aspects of the role of cholesterol in atherosclerosis lies ahead of us before solution is reached. What present knowledge affords us is a fundamental approach for future research—the approach embodied in what

we have termed the cholesterol concept of atherogenesis. In this direction, we predict, lies the solution of the atherosclerosis problem, and with it the eventual control and elimination of this malevolent disease.

This report is based on the work of a large team which over the last 10 years has included Doctors L. C. Akman, S. A. Carlen, D. V. Dauber, M. Feldman, Jr., G. Gros, R. Harris, L. Horlick, M. Hurwitz, M. Lowenthal, R. S. Megibow, A. J. Miller, R. Pick, S. Rodbard, A. Sanders, J. G. Schlichter, E. N. Silber and J. Stamler and the following technicians: L. Adams, E. Arnold, C. Bolene, G. Crowley, M. Dudley, W. Foote, L. Friedberg, L. Havel, P. Johnson, E. Levinson and J. Meyer.

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Human Atherosclerosis and the Diet

By ANCEL KEYS, PH.D.

DISCUSSIONS about the possible effects of the diet on the development of human atherosclerosis center on five items: (1) calorie excess and the resulting obesity, (2) cholesterol in the diet, (3) animal fats in the diet, (4) total fats in the diet, (5) the dietary supply of substances which may have a "lipotropic" action, for example, lecithin, choline, inositol. Since the data on the possible action in man of the lipotropic substances pertain to pharmacologic rather than dietary levels and, moreover, are either questionable or negative in regard to an effect on atherosclerosis, the present discussion will not make further mention of these substances.

There are abundant actuarial data which show there is an elevated incidence of fatal atherosclerosis in obese or overweight people. Routine necropsy studies indicate a direct relationship between atherosclerotic changes in the arteries, including the deposition of cholesterol and lipids, and relative fatness of the whole body. Experiments on the production of atherosclerosis in animals likewise show that the relative calorie intake is important.[3] But atherosclerosis occurs in many persons who are neither fat nor overweight. Our first real conclusion, then, is that the development of the atherosclerotic process is abetted, at least in some persons, by an excessive calorie intake and/or the resulting obesity. The calorie level of the diet is an influential but not a controlling factor.

At present the greatest concern about the diet in regard to atherosclerosis has to do with the consumption of foods which contain cholesterol. In some animals, notably the rabbit and the chicken, the addition of large amounts of cholesterol to the diet can lead to high serum cholesterol concentrations and to arterial lesions which resemble human atherosclerosis in many respects.

Unfortunately, these animal experiments do not necessarily have any relevance to the question of the role of the diet in human atherosclerosis. No animal species close to man in metabolic habitus has been shown to be susceptible to the induction of atherosclerosis by cholesterol feeding. The nearest approach to metabolic comparability is the dog which requires extensive thyroid damage as well as tremendous amounts of dietary cholesterol before positive effects can be elicited. Moreover, even in the favorite species for such experimentation, the herbivorous rabbit, the necessary concentration of cholesterol in the diet is fantastically high in comparison with actual human diets. The actual range of daily intakes of cholesterol provided by real human diets is from zero to perhaps 1000 mg., but the vast majority of human diets seldom average as much as 700 mg. The cholesterol levels in the diets used to induce atherosclerosis in animals range from 0.5 to 5 per cent by weight of the dry food, the most popular level being 2 per cent. This means something like 1000 to 10,000 mg. of cholesterol per 1000 Calories of food, the 2 per cent cholesterol level being equivalent to about 4000 mg. per 1000 Calories if 30 per cent of the calories are derived from fats. We should have to provide some 10,000 to 15,000 mg. of cholesterol daily to a man to be comparable. Moreover, there is reason to believe that man has a greater power of cholesterol regulation than does the rabbit or the chicken. From the animal experiments alone the most reasonable conclusion would be that the cholesterol content of human diets is unimportant in human atherosclerosis.

Direct evidence on man in this connection is unimpressive. Arguments about the incidence of atherosclerosis and the customary intake of cholesterol in the Far East are based on no real data on either atherosclerosis incidence or the character of the diet. The recent analysis of mortality data in Scandinavia[10] is more acceptable but still suffers from the inherent weakness of attempting to discover causation from a parallelism between crude estimates of national averages for two variables. Besides

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the dubious point of attributing war-time changes in vital statistics to actual changes in atherosclerosis, the analysis glosses over the fact that the presumed variations in cholesterol intake were parallel to similar variations in total dietary fat and, at least to some extent, to changes in calories intake and physical activity (see also[13]).

Such, in substance, is the actual evidence on human atherosclerosis itself. But significant inferences can be made from indirect evidence if we admit that there is an important relationship between atherosclerosis and the concentration of cholesterol in the serum. There is overwhelming evidence for such a relationship:

(1) On the average, wherever the serum cholesterol tends to be high—as in diabetes, nephrosis, hypothyroidism, and idiopathic hypercholesterolemia—there is a tendency toward early and severe atherosclerosis.

(2) Persons with definite evidence for disease of the coronary arteries tend to have elevated serum cholesterol values[4] especially when they are compared with properly matched "normals."[5] Good confirmation can be obtained from recent raw data.[6, figs. 14, 15]

(3) There is at least some parallelism between the age trend of cholesterol concentration in the serum and the age trend in atherosclerosis development.[7, 9]

(4) In animal experiments there is a close parallelism between the serum cholesterol level and the development of experimental "atherosclerosis."

There is much new evidence on the effect of the diet on the serum cholesterol level in man. In the first place, the serum cholesterol level of man is independent of large differences in the habitual voluntary intake of cholesterol.[7, 8] Several important confirmations of this fact have been published recently.[4, 14] Colossal intakes, however, far beyond those possible in natural diet, may cause a slow rise in the serum cholesterol.[12]

The rice-fruit diet, which is devoid of both fats and cholesterol, produces a prompt fall in the serum of men with normal levels of cholesterol[2] and a dramatic fall in patients with severe idiopathic hypercholesteremia.[8] We have found that the addition of vegetable fat to this cholesterol-free diet is followed by an equally dramatic rise of serum cholesterol to previous levels.

We have been able recently to make systematic studies on these questions with men under full supervision on diets rigidly controlled for some four months. Starting (and ending) with standard diets providing daily intakes of 150 Gm. of fat and 600 to 700 mg. of cholesterol, the following findings emerged:

(1) Change to a diet devoid of cholesterol and providing 15 Gm. of fat daily produced a rapid fall in serum cholesterol to about 80 per cent of the control value.

(2) Almost identical results were obtained with the same diet to which had been added about 500 mg. of cholesterol daily.

(3) Change to a diet devoid of cholesterol but providing about 70 Gm. of fat daily, produced a decline in serum cholesterol about half as great as when the fat level was only 15 Gm. (No. 1, above).

(4) The addition of 500 mg. of cholesterol daily to the diet (No. 3, above) providing 70 Gm. of fat did not change the result.

It should be noted that all of these experimental diets were comparable in calories and proteins, that the differences in fat intake were achieved by changing the amount of vegetable fat in the diet, and that the differences in cholesterol intake were achieved by adding or withholding whole egg yolks (from which cholesterol is readily absorbed). Finally, with each of the diets the major change in serum cholesterol occurred in the first week or so, and there was a tendency to reach a plateau, or at least a much slower rate of change, in subsequent weeks.

Much longer-term experiments on man are desirable but, so far as they go, these data are consistent within themselves and with all other facts known to me. The ensemble points strongly to the conclusion that, other things being equal, the serum cholesterol level in adult man is independent of the cholesterol intake over the range of zero to at least 700 mg. daily. But the fat intake is quite another

matter and appears to have great importance. However, there is not the slightest evidence for a difference between animal and vegetable fats in this regard.[1]

It is now well recognized, and should have been clear long ago, that all animals, including man, have a large capacity for synthesizing cholesterol. Our experiments on fat-free diets also show that man has a large capacity to remove the cholesterol already present in the blood serum. On such diets the rate of removal of cholesterol from the serum seems to be proportional to the initial (control) serum level of cholesterol. In one patient with hypercholesteremia (900 mg. per 100 ml. of serum), the rate of disappearance from the blood was about 1500 mg. daily for several weeks on a fat-free diet. But with the same cholesterol-free diet to which were added about 50 gm. of vegetable fat, there was an increase of cholesterol in his total serum amounting to about 1000 mg. a day for a period of several weeks.

Now, clearly the cholesterol level is not the whole story in the development of atherosclerosis; otherwise the patient mentioned above would have been dead long ago. But, in so far as there is an important relationship between serum cholesterol and atherosclerosis, these dietary data have both theoretic and practical implications of some consequence.

A final question may be raised about the significance of all this in view of the studies by Gofman and his colleagues on the materials separated in the ultracentrifuge. From the evidence reported so far we may make two comments and draw a tentative conclusion:

(1) The response to diet of the serum concentration of substances characterized by −10 to −20 Svedberg units of sedimentation (the "G" substances) appears to be similar to our findings with serum cholesterol, and

(2) There is as yet no reason to suggest that the concentration of G substances in the serum is any more closely related to atherosclerosis than is the concentration of total cholesterol.

(3) At present, we may conclude that the implications for atherosclerosis drawn from dietary effects on serum cholesterol would be similar if the serum criterion were the concentration of the G substances.

In summary, then, we may remark that direct evidence on the effect of the diet on human atherosclerosis is very little and is likely to remain unsatisfactory for a long time. But such evidence as there is, plus valid inferences from indirect evidence, suggests that a substantial measure of control of the development of atherosclerosis in man may be achieved by control of the intake of calories and of all kinds of fats, with no special attention to the cholesterol intake. This means: (1) avoidance of obesity, with restriction of the body weight to about that considered standard for height at age 25; (2) avoidance of periodic gorging and even temporary large calorie excesses; (3) restriction of all fats to the point where the total extractable fats in the diet are not over about 25 to 30 per cent of the total calories; (4) disregard of cholesterol intake except, possibly, for a restriction to an intake less than 1 Gm. per week.

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Blood Lipids and Human Atherosclerosis

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PREVIOUSLY evidence has been presented relating certain serum lipoproteins to the development of atherosclerosis in man.[1-3] Further studies now enable us to make quantitative estimations of the relationship of certain aspects of lipid transport via lipoproteins with atherosclerogenesis, including follow-up studies. There are several points of evidence which have led us to an understanding of this derangement of blood lipoproteins from the "normal" pattern. The first observation of derangement of the lipid transport mechanism was made on serum lipoproteins of rabbits subsequent to their development of hypercholesteremia by cholesterol feeding.

In the course of cholesterol feeding, molecules of high S_f classes, S_f 10–30, 30–100, and higher (of higher molecular weight, lower density, higher lipid content and lower protein content than the normally occurring lipoproteins) appear in the serum, in contrast to the normal lipoproteins which are in the class of S_f 10 and below. There is differential significance to the presence of these several lipoproteins which appear in the serum under several types of experimental conditions inducing hypercholesteremia. For the rabbit there is no relation between the serum levels of S_f 10 and lower and atherosclerosis[1] during active atherogenesis. A lack of positive relationship between S_f 10 and lower molecules and atherosclerosis has been significantly demonstrated ($r \cong -0.32$).

Some of these observations were on rabbits which received potassium iodide in addition to cholesterol feeding. Under this condition the increase in serum cholesterol and serum lipids is primarily in the S_f 10 and lower fraction, which is elevated as high as or higher than in the cholesterol-fed rabbit that develops atherosclerosis. In fact, severe atherosclerosis often develops with low levels of this class of lipoproteins, whereas no atherosclerosis develops in spite of several fold increase in concentration of such lipoproteins. However, there is a high relationship (correlation coefficient $\cong +0.8$) between estimated degree of atherosclerosis as measured at autopsy and the concentration of lipoproteins of the S_f 10–30 class when it develops *regardless* of the experimental condition. This observation is drawn from rabbits which were rendered hypercholesteremic by: (a) cholesterol feeding, (b) cholesterol and oil feeding, (c) cholesterol and potassium iodide feeding, and (d) cholesterol and oil feeding in the alloxanized rabbit. (Each of these experimental types has a differential alteration of the serum lipoproteins). Under certain uniform conditions such as cholesterol or cholesterol and oil feeding there is an excellent quantitative relationship between degree of atherosclerosis and the total blood cholesterol. However, this is only due to the fact that the S_f 10–30 molecules account in this case for the main proportion of the increase in total serum cholesterol. That the total blood cholesterol itself is not the important feature has been clearly demonstrated by Pierce[4] in our laboratory, studying the Duff[5] type of alloxanized rabbit. Duff has previously shown that feeding cholesterol to alloxan diabetic rabbits results in elevation of serum cholesterol to levels over 2000 mg. per 100 cc. with a much less severe atherosclerosis developing than in the normal cholesterol-fed rabbit at comparable and much lower total cholesterol levels. Pierce has shown that in the Duff type rabbit the cholesterol is transported primarily in the

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form of molecules of the S_f 100 and higher classes. Some of the Duff type rabbits develop atherosclerosis, but they are the ones which also develop large amounts of S_f 10–30 molecules as well as the S_f 30 and higher molecules. Recently Graham and co-workers[6] in this laboratory maintained cholesterol- and oil-fed rabbits on daily injections of heparin (10 mg. per kilogram per day). Heparin minimizes a rise in the concentration in the S_f 10–30 class of molecules by facilitating the formation of lower S_f classes of lipoproteins. These rabbits are markedly protected from atherosclerosis even though they are exposed to a metabolic burden of fat (3 Gm. per day) and cholesterol (1 Gm. per day) which ordinarily produces atherosclerosis.

It appears therefore that high levels of S_f 10–30 lipoproteins are consistently associated with atherosclerosis in the rabbit, whereas no association can be established for the S_f 100 and higher and the S_f 10 and lower classes. Serum cholesterol can be used as a partial guide *only* under the special conditions where the S_f 10–30 molecules are relatively greatly increased. If cholesteremia in the Duff-alloxan type rabbit and the Anitschkow-cholesterol-fed rabbit is compared with atherosclerosis, a significant *negative* relationship will actually be found between atherosclerosis and serum cholesterol. As will be discussed later, each of the different types of rabbit hypercholesteremia, (1) the Duff-alloxan type with its increment of increased cholesterol primarily in the lipoproteins greater than S_f 100; (2) the Anitschkow-cholesterol-fed type with its increase first in the S_f 10 and lower; and (3) the later stage of cholesterol or cholesterol and oil feeding (with the bulk of cholesterol carried in the S_f 10–30 class of lipoproteins), has its counterpart in types of human sera which are probably of similar differential significance (see fig. 1).

Preliminary studies (with the cooperation of Kendall[7] and Chaikoff[8]) on hypercholesteremic-atherosclerotic dogs and chickens indicate that there is a similar shift in both species of the serum lipids to higher S_f lipoproteins than exist normally. It must still be determined, through a more extensive study, which special class may be involved in these species, although it is known that the S_f 10–30 class becomes elevated in both dog and chicken.

A detailed account of the chemical composition and physical nature of the lipoproteins composing the lipid transport system has appeared.[3, 9, 10] Each of the lipoproteins (at least nine discrete components up to S_f 17 and a host of unresolved components above S_f 20 have been observed) contains cholesterol, phospholipid and protein, but in different amounts. Those lipoproteins above S_f 13 contain neutral fat also. Since each lipoprotein can vary in concentration in a semi-independent way, there is no assured relationship between total serum cholesterol or phospholipid or fat and the concentration of any particular lipoprotein species. We have seen no higher correlation than $r \leqq 0.4$ to 0.5 between serum cholesterol and any one of these lipoprotein components or between the individual lipoprotein classes. It is the purpose of this paper to evaluate quantitatively the relationship that does exist between total serum cholesterol and the certain classes of lipoproteins in the human and the relation of each to atherosclerosis. We have previously indicated that elevation of the S_f 12–20 lipoproteins,[3, 11] is part of a lipid metabolic defect which is often associated with elevations in level of the S_f 20–100 class of lipoproteins. Further, there are many individuals who have inordinately high S_f 20–100 levels at a modest S_f 12–20 level. (See later section concerning S_f 12–20 intercorrelation with lipoproteins above S_f 20.) In humans with less severe degrees of the metabolic error, S_f 20–100 levels fluctuate acutely with reference to ingestion of fat. However, in those with severe degrees of the metabolic error the S_f 20–100 class is elevated even postabsorptively.[11] Until now we have refrained from using the lipoproteins higher than S_f 20 as a correlative guide because of the greater fluctuations in concentrations of these lipoproteins than occurs in the S_f 12–20 class. In spite of the variability in levels of molecules from S_f 20–100, it has now become evident, as will be explained below, that these molecules are strongly related to atherosclerosis and represent an independent

contribution to accountability for atherosclerosis, in addition to the already established association of the S_f 12–20 class of lipoproteins with atherosclerosis. It should be pointed out that the intercorrelation between the S_f 12–20 and the S_f 20–100 classes of lipoproteins is relatively low, and it is common to see severe disproportion in the concentration of S_f 12–20 and S_f 20–100 classes. Atherosclerosis is associated with elevated levels of either class of lipoproteins, and since the intercorrelation of the two classes is low, a significant improvement in identification of atherosclerogenic states results from consideration of the entire S_f 12–100 class of lipoproteins (that is, the sum S_f 12–20 and S_f 20–100).

The entire S_f 12–100 class of lipoproteins represents only about 10 to 15 per cent of all the serum lipoproteins and contains approximately 10 to 15 per cent of the total serum cholesterol. As will be shown in analysis of the data below, it is the cholesterol within the S_f 12–100 lipoproteins that represents the entirety of the association of cholesterol with atherosclerosis. Since this amount is such a small fraction of the total cholesterol, and is so poorly related to the remaining 85 to 90 per cent of the cholesterol, it is largely masked in the routine determination of total serum cholesterol, even if the latter measurement is done with great accuracy.

In this report we have studied two groups:

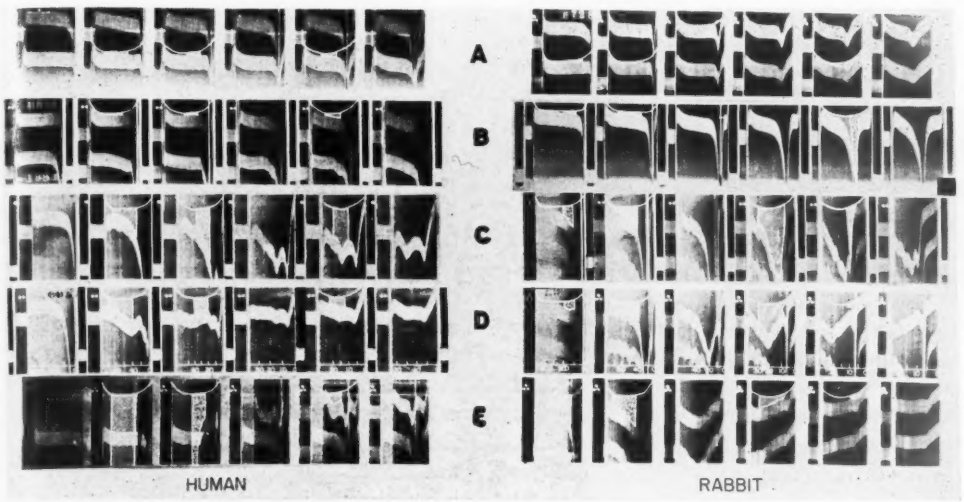

FIG. 1. Ultracentrifugal flotation patterns, showing the increase in the lipid metabolic defect in the human and the experimental rabbit. In all these figures the S_f rates can be read off the S_f scale placed on all frames; concentrations of various lipoprotein fractions are proportional to the shaded areas. *A* shows the flotation pattern of a normal child and a normal rabbit, both having low concentrations of lipoproteins below S_f 10 and trivial concentrations above S_f 10. *B* shows the patterns for a normal human and for a rabbit with elevation of the concentrations of lipoproteins below S_f 10 but without appreciable elevations of lipoproteins of higher S_f classes. *C* shows corresponding patterns for human and rabbit with moderate concentrations of lipoproteins of S_f 10 and less, but with great elevations in the S_f 12–20 and 20–40 classes in the human and S_f 10–30 class in the rabbit. This rabbit developed marked atherosclerosis. *D* shows analogous patterns for human and rabbit with marked elevation of S_f 12–20 class in human and S_f 10–30 class in rabbit, but with depression of the concentration of lipoproteins of S_f 10 and less. This rabbit also developed marked atherosclerosis. *E* shows the manifestation of severe lipid metabolic error in human and rabbit. Note the low concentration of lipoproteins below S_f 10, moderate concentration of lipoproteins of S_f 12–20 class in the human and S_f 10–30 class in the rabbit, and high concentration of lipoproteins from S_f 20–100 in both human and rabbit.

(1) patients with coronary artery disease manifested by either myocardial infarction or classic angina pectoris, and (2) individuals who are presumably normal in that they show no clinical sign of atherosclerosis and are in active physical condition normal to their mode of living. While other diseases with atherosclerotic complications are discussed, particular use is made of coronary artery disease, for it can be diagnosed with a high degree of reliability. This criterion group is manifesting a complication of atherosclerosis of the coronary arteries in an estimated 90 to 95 per cent of cases.[2] Among normal persons, atherosclerosis is consistently reported with high occurrence rate from autopsy reports.[12] Presumably, for many years of evolution of the atherosclerotic state, there was no external sign of the disease. It is estimated that in any group of supposedly normal, adult men, 30 to 50 per cent may be actively developing arterial atheroma.[11] Statistical comparisons made between presumed normals and atherosclerotics are, in their crude form, of limited quantitative interpretation, since they contrast a population about 95 per cent atherosclerotic to a population 50 to 80 per cent "true normal" admixed with 50 to 30 per cent atherosclerogenic normal. However, it is possible to estimate a correction for the impurity of the latter criterion group, as will be described in a later section.

We have studied 253 normal men and 93 men with coronary artery disease, all between the ages of 41 and 50 years. Of the coronary group, 75 were men studied at least six weeks after a myocardial infarction and 18 were men manifesting typical angina pectoris. In another group of men between the ages of 51 and 60 years 149 were normal and 126 had coronary disease; in this coronary group there were 110 survivors of myocardial infarction and 16 patients with typical angina pectoris. There were no significant differences in lipoprotein or cholesterol levels between the cases with angina and those with myocardial infarction, so in each age group both types were combined as "patients with coronary artery disease" for purposes of analysis.

Several approaches were made to the analysis of the data in an effort to assess the relationship S_f 12–20 and S_f 20–100 lipoproteins and of total serum cholesterol to atherosclerosis. Over-all relationships and the relationship of each measure independent of the others were evaluated previously[11]; it was demonstrated that the S_f 12–20 lipoprotein levels were consistently two to four times as effective as the serum cholesterol level in segregating atherosclerotics from normals. It became apparent in those data that there was a slight residual association of serum cholesterol levels with atherosclerosis in the 41 to 50 year age group, even when the relationship of S_f 12–20 lipoprotein levels with atherosclerosis was taken into account. This suggested the probable existence of certain additional lipoprotein classes independently associated with atherosclerosis. The current analysis confirms the association of certain lipoproteins (the S_f 12–20 and S_f 20–100 classes) with atherosclerosis and the exclusion of other lipoproteins from such association. The analysis shows further that the total serum cholesterol level is associated with atherosclerosis only through its weak relationship with the important S_f 12–20 and S_f 20–100 classes of lipoproteins. When individuals are evaluated at the same combined level of lipoproteins of the S_f 12–100 class (S_f 12–20 plus S_f 20–100), there is *no* residual relationship of the remaining bulk ($\sim$ 85 to 90 per cent) of the serum cholesterol with atherosclerosis, even in individuals with marked hypercholesteremia. Serum cholesterol measurements permit only a slight segregation of atherosclerotics from normals in the age group under 50 years, and permits no segregation of the atherosclerotic group from the normal group above the age of 50 years. Overall, a serum cholesterol determination tends more to obscure than to clarify the status of an individual with respect to atherosclerosis. By contrast, the S_f 12–100 lipoprotein determination offers a continuous scale of positive association with atherosclerotic activity, no matter whether the serum cholesterol is low, moderate, or high.

Analysis of the Relationship of S_f 12–20 and S_f 20–100 Lipoproteins and of Serum Cholesterol to Atherosclerosis

The literature concerning serum lipids is marked by great differences which are the result both of nonuniformity of populations sampled and of technical differences in laboratory procedures of analysis. It is ridiculous to contrast serum lipid analyses between groups without rigorous control of both of these sources of variation in reported lipid concentration. For this study it has been an absolute requirement to determine both lipoproteins and total serum cholesterol on the same serum sample under controlled laboratory conditions. This approach permits a direct comparison between these two types of lipid analysis as to their association with atherosclerotic tendency.

Table 1 provides a summary of the pertinent data for the various lipoprotein classes measured and for the total serum cholesterols in the 41 to 50 and 51 to 60 year age groups considered. These data are requisite to a further evaluation of the association of any of the measures with atherosclerosis. It is evident that for the 41 to 50 year age group, all three measures, the S_f 12–20 level, the S_f 35–100* level, and the total serum cholesterol level, are significantly higher in patients with coronary artery disease than in normal persons. The first crude assessment of the association of each measure with atherosclerosis can be made by comparing the difference in mean levels (between the normal and coronary group) with reference to the standard deviation of the distribution of values for each measure. Thus it is seen that the greatest relative difference established for normal subjects and coronary patients 41 to 50 years old is in the combined S_f 12–20 and S_f 35–100 lipoprotein measure. Next is the separation achieved by the S_f 35–100 lipoprotein measure.

Table 1.—*Lipoprotein and Cholesterol Measurements in Normal Subjects and Patients with Coronary Artery Disease*

	41–50 Year Age Group (Males)		51–60 Year Age Group (Males)	
	Normal Subjects	Coronary Disease Patients	Normal Subjects	Coronary Disease Patients
No. Cases	253	93	149	126
Mean S_f 12–20 Lipoprotein Level	45 ± 27	71 ± 32	46 ± 21	70 ± 31
Mean S_f 35–100 Lipoprotein Level	64 ± 49	120 ± 74	61 ± 45	92 ± 65
Mean Combined S_f 12–20 + S_f 35–100 Lipoprotein Level	109 ± 65	191 ± 93	107 ± 57	162 ± 79
Mean Serum Cholesterol Level	260 ± 63	297 ± 68	274 ± 65	286 ± 69
Intercorrelations*				
S_f 12–20 vs. Chol	0.40	0.39	0.23	0.25
S_f 35–100 vs. Chol	0.3	0.13	0.0	0.0
S_f 12–20 vs. S_f 35–100	0.41	0.54	0.44	0.38

All values are given plus or minus the standard deviation of the distribution.

* Coefficients of correlation are expressed as Pearson *r*.

An almost equivalent separation exists for the S_f 12–20 lipoprotein measure. The poorest separation exists for the serum cholesterol measure. The actual values of the quotient of difference in means by the σ for each measure is given in table 2.

Consideration of the ratios in table 2 reveals that for the 41 to 50 year age group measurement of either S_f 12–20 or S_f 35–100 lipoprotein segregates patients with coronary disease from normal subjects with high efficiency. The best segregation of coronary disease patients from normal subjects is achieved by combining the S_f 12–20 and S_f 35–100 lipoprotein values. Since the contribution of the S_f 12–20 and S_f 35–100 measures are in large part independent of each other, it is under-

* S_f 20–100 class equals S_f 20–35 plus S_f 35–100. As discussed in the text, the independent contribution of S_f 20–35 is small; it is omitted from this analysis.

standable that the combination is superior to either alone. Individually and combined the lipoprotein measurements are highly superior to serum cholesterol measurement in segregating coronary disease patients from normals. In fact, in the 51 to 60 year age group the serum cholesterol measurement cannot be shown to produce any significant segregation of the coronary disease group from the normal group.

TABLE 2.—*Crude Segregation of Patients with Coronary Disease and Normals by the Lipoprotein and Cholesterol Measures*

	Difference in Means (Coronary Disease − Normals)	Standard Deviation of Normal Distribution	Ratio, Difference in Means: Standard Deviation
41–50 Years			
	mg. per 100 cc.	*mg. per 100 cc*	
Combined S_f 12–20 + S_f 35–100	82	65	1.3
S_f 35–100	56	49	1.1
S_f 12–20	25	27	0.9
Serum Cholesterol	37	53	0.7
51–60 Years			
Combined S_f 12–20 + S_f 35–100	55	57	1.0
S_f 35–100	31	45	0.7
S_f 12–20	24	21	1.1
Serum Cholesterol	12	65	0.19

A simple method of measuring the association of each factor (that is, S_f 12–20 level, S_f 35–100 level, or serum cholesterol level) independently with atherosclerosis is achieved by comparing the lipoprotein segregating ability at any particular serum cholesterol level, and conversely the serum cholesterol segregating ability at any particular lipoprotein level. Thus, there are given in figure 2 *A*, *B*, *C* the average values of S_f 12–20 and S_f 35–100 lipoprotein levels for every part of the serum cholesterol range, for both normals and patients with coronary artery disease. It is evident that the patients with coronary artery disease show essentially the same elevation of S_f 12–20 and S_f 35–100 lipoproteins above normal levels when compared *at the same cholesterol level* throughout the entire cholesterol range. This is equivalent to matching each patient with coronary disease with a normal who has the same cholesterol level. Conversely, the data of figure 2*C* can be used to compare the serum cholesterol level in patients with coronary disease with the level in normal persons at the same lipoprotein level. It is seen that when individuals in the coronary group are matched with normals having the same lipoprotein levels there is no significant difference in cholesterol level, indicating that cholesterol level of itself does *not* segregate coronary and normal populations independently of its weak association with the lipoprotein classes (S_f 12–20 and S_f 35–100) which are truly associated with atherosclerosis. For the two age groups studied, the actual data obtained in such comparisons are given below.

Comparison of S_f 12–20 and S_f 35–100 Lipoproteins in Coronary Disease Patients and in Normal Subjects at Identical Cholesterol Levels

From the data shown in figure 2 *A*; *B*, *C* it can be seen that 41 to 50 year old patients with coronary disease average higher than normal in (S_f 12–20 plus S_f 35–100) lipoproteins by 69 mg. per 100 cc., higher in S_f 35–100 lipoproteins by 51 mg. per 100 cc., higher in S_f 12–20 lipoproteins by 18.0 mg. per 100 cc.; all comparisons are with normal subjects at equal cholesterol levels. Patients 51 to 60 years old with coronary artery disease also show equivalent elevations, namely 22 mg. per 100 cc. higher in S_f 12–20 lipoproteins than equivalent normals for the same cholesterol level.

Comparison of Cholesterol Levels at Corresponding Serum Lipoprotein Concentrations

In the 41 to 50 year old group of patients with coronary artery disease, cholesterol is only 17 mg. per 100 cc. higher than in normals compared at the same S_f 12–20 level. This small residual elevation is completely lost when coronary and normal populations are contrasted at the same (S_f 12–20 plus S_f 35–100)

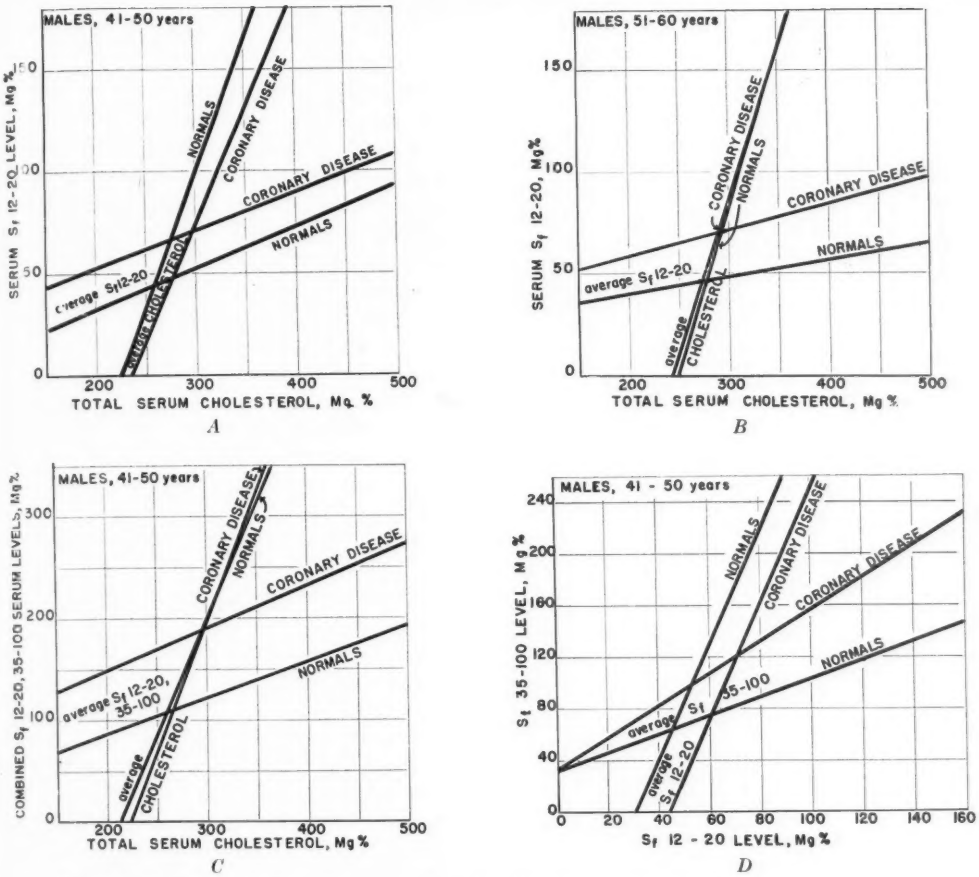

FIG. 2*A*, *B*, *C*. In each diagram separate lines indicate the normal subjects and the coronary disease patients. The lines marked "average cholesterol" indicate the value of the serum cholesterol for a sample of the population chosen at a precise lipoprotein level (either S_f 12–20 or the sum of S_f 12–20 and S_f 35–100, depending upon which plot is considered). The lines marked "average S_f 12–20" indicate the value of the lipoprotein level for a sample of the population chosen at a precise cholesterol level.

These plots show explicitly that the S_f 12–20 or S_f 12–20 plus S_f 35–100 lipoproteins can consistently separate the coronary disease population from the normal population, regardless of the cholesterol level encountered. Shown equally well is the failure of the serum cholesterol level to separate consistently the coronary disease population from the normal population, when these populations are compared at a given lipoprotein level.

D. These plots show the equivalent and independent segregating ability of both the S_f 12–20 and the S_f 35–100 lipoprotein levels for coronary and normal populations.

In all plots the intersection of the two normal curves, or of the two coronary disease curves, gives the mean values for the population concerned; for example, in 2*A*, the mean serum cholesterol and mean S_f 12–20 levels.

levels; the coronary population is 1 mg. per 100 cc. of cholesterol lower than normals of the same (S_f 12–20 plus S_f 35–100) levels.

In the 51 to 60 year old group, patients with coronary artery disease are likewise unsegregated from normal subjects by cholesterol when cholesterol levels are compared at the same S_f 12–20 level.

Thus it is apparent that lipoproteins of the S_f 12–100 class are highly associated with the atherosclerotic state and that total serum cholesterol is only related to the extent that the small fraction of cholesterol (contained in these particular lipoproteins) can influence the bulk of total serum cholesterol. Inasmuch as approximately 90 per cent of total serum cholesterol is unassociated with atherosclerosis, gross deception is usually to be expected in attempting to evaluate atherosclerosis from the serum cholesterol level on the individual basis. A patient with high atherosclerotic activity will frequently be completely misdiagnosed because his serum cholesterol is moderate or low; conversely, there are many hypercholesteremic individuals who are falsely evaluated as having high atherosclerotic activity. Both of these errors will in general be avoided if the truly atherosclerogenic lipoproteins are used as a clinical guide, rather than the serum cholesterol level.

Figure 2*D* shows clearly the independent association of the molecules of the S_f 35–100 lipoproteins with atherosclerosis. Even though the S_f 35–100 lipoprotein level is partly related to the S_f 12–20 level, the S_f 35–100 level is higher in patients with coronary artery disease when both normal and atherosclerotic persons are compared at the same S_f 12–20 level. Conversely, the S_f 12–20 level is associated with atherosclerosis independently of its partial relation to S_f 35–100 levels.

The S_f 20–35 class of lipoproteins is also somewhat independently associated with atherosclerosis; however, it is related to both the S_f 12–20 class and the S_f 35–100 class. Hence very little additional gain in assessing atherosclerotic potentialities can be made by including this fraction. A more extensive analysis of our data will be necessary to establish the most effective means of assigning relative weights to the various lipoproteins within the S_f 12–100 class. For the present, due to the larger fluctuation of the S_f 35–100 class, it is advisable to regard the S_f 12–20 and S_f 35–100 classes separately and combined. This does not imply that the S_f 35–100 is of less significance, but rather that its variability may be obscuring an even stronger relationship.

Hypercholesteremic States and Atherosclerotic Activity

Hypercholesteremia (levels over 300 mg. per 100 cc.) has long been considered to be associated with atherosclerosis. However, there is reason to believe that there are differences in atherosclerotic activity even among the hypercholesteremics. To study this question we have compared all the normal subjects (134 cases) having serum cholesterol levels over 300 mg. per 100 cc. with all the patients with myocardial infarction (90 cases) of corresponding age and sex. A slight adjustment between the two groups, correcting to the same serum cholesterol level, was made using the regression equation. (Actual serum cholesterol mean for coronaries was 355; for normals, 347.) When patients with infarcts are compared with normals, both at the same mean cholesterol level (355 mg. per 100 cc.), the S_f 12–20 level in the myocardial infarct group is 89.5 mg. per 100 cc., while that of the normal group is 64.5 mg. per 100 cc. The difference of 25 mg. per 100 cc. is highly significant ($p <$ 1 per cent).

If the data for the normals are corrected by the regression equation so that the S_f 12–20 levels are equal in the myocardial infarct and normal groups, the mean cholesterol is not higher in those with infarcts than in the normals.

Of special interest, because of its exceptionally high atherosclerotic activity, is the group manifesting the syndrome xanthoma tuberosum. These patients are quite uniformly hypercholesteremic, but appear to have manifestations of atherosclerosis in excess of what might be anticipated for their degree of hypercholesteremia. Twelve cases of xanthoma tuberosum were matched with hypercholesteremic normals.

The serum cholesterol of the 12 cases of xanthoma ranged from 275 mg. to 640 mg. per 100 cc., averaging 489 mg. per 100 cc. The S_f 12–20 lipoproteins in these cases ranged from 76 mg. per 100 cc. to 520 mg. per 100 cc., averaging 250 mg. per 100 cc. The closest matched group of hypercholesteremic normals that was possible showed a range of 423 to 492

mg. per 100 cc. serum cholesterol, averaging 447 mg. per 100 cc. The S_f 12–20 lipoproteins ranged from 48 mg. per 100 cc. to 99 mg. per 100 cc., except for one case at 300 mg. per 100 cc., and averaged 85 mg. per 100 cc. A slight correction of the normal group to serum cholesterol level identical with the xanthoma patients was made by use of the regression equation. The equivalent normals at 489 mg. per 100 cc. serum cholesterol would have an S_f 12–20 level of 96 mg. per 100 cc. Thus, the extraordinary atherosclerotic tendency of patients with xanthoma tuberosum is explainable because their level of S_f 12–20 lipoproteins is about two and one-half times higher than even equivalently hypercholesteremic normals.

The Accountability for the Atherosclerotic State from Lipoprotein Measurement

In a previous paper,[11] by the technic of biserial correlation, we have estimated roughly the extent of accountability for the atherosclerotic state that can be drawn from the measurement of these serum lipoproteins. These correlation technics are not being used to establish the independent significance of the lipoproteins in atherosclerosis, but rather in an attempt to assess how closely these lipoproteins account for the totality of factors which lead to atherosclerosis. An estimation has been made of the biserial correlation coefficient for the combined S_f 12–20 and the S_f 35–100 measurement with atherosclerosis for the 41 to 50 year age group reported in this paper. This biserial r is 0.57. Ideally one may square such a correlation coefficient to obtain the fraction of the total variance (which is unity) that has been accounted for directly. In this case the total S_f 12–20 and S_f 35–100 have accounted for about four-tenths of factors associated with atherosclerosis. The serum cholesterol measurement contributes nothing further to this estimate. There are limitations to the general use of the biserial technic in an absolute sense in situations of this type; these have been discussed fully in an earlier paper.[11] For, whatever quantitative methods are used to establish relationship between these serum lipoproteins and atherosclerosis, certain factors will always preclude complete accountability of the true relationship that exists. Among these factors are the following:

(1) *Accumulated Atherosclerosis vs. Atherosclerotic Activity*

Measurement of derangement of lipid metabolism by S_f 12–20 lipoprotein molecules is thought to indicate *active* atherosclerogenesis. Is myocardial infarction caused by *active* or *accumulated* atherosclerosis? If it is primarily a disturbance of accumulated atheroma, then angina or myocardial infarction is not a pure criterion of active atherosclerosis and is of value only through the relationship of degree of atherosclerosis to rate of accumulation of atherosclerosis. This error has not been estimated and cannot be estimated at this time.

(2) *The Impurity of the "Normal" Population*

The normal population is composed of a group of true normals whose atherosclerotic activity is insufficient to produce significant atherosclerosis, and normals whose atherosclerosis has not yet advanced to clinically detectable levels or to manifest complications of atherosclerosis. It is variously estimated that 30 to 50 per cent of normals are moderately to severely atherosclerotic.[12]

(3) *Focal Factors in Atherosclerosis*

The focal character of atherosclerosis, especially when of mild degree, is indisputable, but this is consistent with the role of lipids in its pathogenesis. It is entirely reasonable that, given the necessary lipid metabolic abnormality, certain susceptible sites will be earlier and more extensively involved. It may well be the case that if such lipid metabolic abnormality is not present, even susceptible focal sites will not show appreciable disease. In this factor alone there can be great individual variation, even though we feel it is justifiable to say that atherosclerosis of the coronary arteries (and its rate of development) will on the average be more pronounced in patients with myocardial infarction than in normals. The exact degree to which this factor prevents accounting for the total variance between atherosclerotic and normal subjects cannot be estimated at this

time. This factor is of importance and it is hoped that follow-up autopsy will enable an assessment of its magnitude.

(4) Reliability, Errors and Consistency of Measurements

Any measured relationships between such factors as total serum cholesterol or S_f 12–20 lipoproteins with atherosclerosis are influenced by errors of measurement and biologic variation with time. Such errors and biologic variation have the effect of reducing the measured relationships, as they have been calculated in this discussion from single measurements on all subjects, normal or atherosclerotic. We have previously made an effort to assess these factors in order that the observed S_f 12–20 or cholesterol relationship to atherosclerosis may be corrected for this attenuation.[11]

The over-all reproducibility from determination to determination on the same individual has a coefficient of reliability of 0.67 $\pm$ 0.05 for S_f 12–20 determination and 0.75 $\pm$ 0.07 for total serum cholesterol determination. (These figures represent the reliabilities over the one-year period during which the data reported in this paper were collected). During the same interval the technical reproducibility of the two measurements showed coefficients of reliability of 0.80 $\pm$ 0.04 for S_f 12–20 measurement and 0.91 $\pm$ 0.001 for serum cholesterol measurement. Therefore it is estimated that the biologic variation during this period is expressed by a coefficient of reliability of $r = 0.84 \pm 0.06$ for S_f 12–20 measurement and $r = 0.82 \pm 0.07$ for total serum cholesterol measurement.

This may be translated into terms of observed biologic variation for the average "normal" (41 to 50 years) whose S_f 12–20 level is 45 mg. per 100 cc. From the standard deviation of the distribution of levels (σ = 27 mg. per 100 cc.) and the reliability coefficient r = 0.84, we calculate a standard error of the obtained value of approximately 10 mg. per 100 cc. S_f 12–20 lipoproteins. For serum cholesterol, the average "normal" whose level is 260 mg. per 100 cc., with a standard deviation of the cholesterol distribution of 63 mg. per 100 cc. and r = 0.82, will show a standard error of the obtained value of 25 mg. per 100 cc. cholesterol. Thus, a single measurement places the average individual within + 10 mg. per 100 cc. S_f 12–20 and $\pm$ 25 mg. per 100 cc. serum cholesterol of his "true" value for that particular year period two-thirds of the time.

For over-all variation, including biologic variation and technical errors of measurement, a single determination has a standard error of the obtained value of 15 mg. per 100 cc. S_f 12–20 and 29 mg. per 100 cc. serum cholesterol. Thus a single measurement places an individual (including both biologic variation and technical error) within $\pm$ 15 mg. per 100 cc. S_f 12–20 and $\pm$ 29 mg. per 100 cc. cholesterol of the "true" values two-thirds of the time.

The crude biserial r found for the S_f 12–20 plus S_f 35–100 lipoproteins gives a correlation with atherosclerosis of approximately $\pm$ 0.57. When corrected for (1) the fact that the populations of "normals" and coronary disease patients are only impurely identified, and (2) technical errors that separate a single determination of serum lipoproteins from its true value, the true biserial r may be much greater than the 0.57 measured and may be sufficiently close to unity to account for all the etiologic factors in this disease.

Significance of S_f 12–20 Lipoprotein Levels in the Prognosis and Management of Atherosclerosis

In the preceding section quantitative evidence has been presented for the relationship of S_f 12–20 lipoprotein levels to atherosclerotic activity. It follows therefore that the S_f 12–20 levels might be of prognostic value in patients with established atherosclerosis, in assessing their present potential of atheroma production, as well as in normals, in predicting their likelihood of developing a clinical manifestation of atherosclerosis. We have sufficient follow-up data now to evaluate both of these possibilities.

Prediction of Occurrence of Myocardial Infarction in the Normal Population

A follow-up study has been in progress for the past one and one-half years to obtain

information on the occurrence of clinical manifestations of atherosclerosis in individuals previously classified as normal and measured for their S_f 12–20 lipoprotein level. At this time we have complete follow-up information from a block of 1500 normal subjects studied. There have been four occurrences of myocardial infarction documented in males previously normal. These occurred at ages 38, 42, 45 and 53 with S_f 12–20 levels of 100, 68, 55, and 52, respectively. At the same ages in the normal group there are 1000 cases, of whom 340 were above 50 mg. per 100 cc. at the time of study and 660 were below 50 mg. per 100 cc. While the number of cases of occurrence of myocardial infarction is small, the chance that the relationship between S_f 12–20 levels greater than 50 mg. per 100 cc. and occurrence of infarction is not significant is only 1 in 50.

In a group of hypertensives (200) that had shown no clinical evidence of atherosclerosis at the time their S_f 12–20 levels were determined, there have now been three occurrences of myocardial infarction at levels of 55, 78, and 145 mg. per 100 cc. These numbers are not significant by themselves, but they further show that the range of 50 mg. per 100 cc. S_f 12–20 and above includes the probable occurrences of myocardial infarction, since 50 mg. per 100 cc. is the 50:50 division of the hypertensive population. There are many uncomplicated hypertensives in the normal S_f 12–20 ranges.

Recurrence of Myocardial Infarction in Patients with Established Coronary Artery Disease

In a group of patients with previously known coronary artery disease, a rate of occurrence of myocardial infarction higher than in a normal population is expected. We have now been able to observe 39 recurrent myocardial infarctions in the over-all coronary disease population (359 cases) for which we have follow-up information over a one year period. Of these recurrences, 36 showed a level of S_f 12–20 lipoproteins at the time of initial study over 50 mg. per 100 cc., and three had levels below 50 mg. per 100 cc. The actual levels in the recurrences were: 210, 156, 136, 130, 125, 116, 114, 114, 109, 101, 100, 97, 92, 88, 88, 88, 88, 85, 84, 84, 84, 83, 78, 78, 76, 76, 65, 65, 64, 62, 62, 61, 54, 52, 51, 50, 44, 43, and 38 mg. per 100 cc. S_f 12–20 lipoproteins.

There are no factors of difference between the over-all nonrecurrence coronary population and the recurrence population, at least with regard to age, physical activity, sex, previous clinical history, or drug therapy. Some of both the recurrence and nonrecurrence group had been on low fat–low cholesterol diets. Since there are no significant differences between the two groups in other respects, it is justifiable to compare them on the basis of their initial S_f 12–20 lipoprotein levels. Considering a level of 50 mg. per 100 cc. S_f 12–20 lipoproteins, 36 of the recurrences were above this level and three were below this level, whereas in the nonrecurrence group 202 were above and 118 were below this level. A test of significance of the relationship of levels above 50 mg. per 100 cc. with recurrence of myocardial infarction indicates there is less than 1 chance in 1000 that this point of segregation is not real. An even more striking difference is seen above 80 mg. per 100 cc. when the recurrence and nonrecurrence groups are contrasted. In the recurrence group 22 cases were above 80 mg. per 100 cc. and 17 cases were below; in the nonrecurrence group, 64 cases were above 80 mg. per 100 cc. and 256 cases were below. A test of the relationship of S_f 12–20 levels above 80 mg. per 100 cc. with recurrence of myocardial infarction indicates there is less than 1 chance in 10,000 that this point of segregation is not real. These results may be converted to another form of some practical predictive value. The data are plotted in figure 3 as the per cent chance of recurrence of myocardial infarction in one year as a function of a single measured level of S_f 12–20 lipoproteins (along with the data for occurrence of myocardial infarction in one year for individuals who have not previously manifested coronary artery disease). The plot indicates that for a patient with coronary artery disease the over-all chance of a recurrence within one year is approximately 17 per cent for an S_f 12–20 level of 100 mg. per 100 cc., whereas it is approximately 6 per cent for an S_f 12–20 level of 50 mg. per 100 cc. These

data show that the prognosis for a patient with coronary artery disease is much worse if the S_f 12–20 lipoprotein level is high than if it is moderate or low.

A study of 49 patients in the acute phase of myocardial infarction shows that the S_f 12–20 lipoprotein level determined during the first week after occurrence (or from autopsy blood for some of the fatal cases) is of prognostic significance here also. The data are presented in table 3.

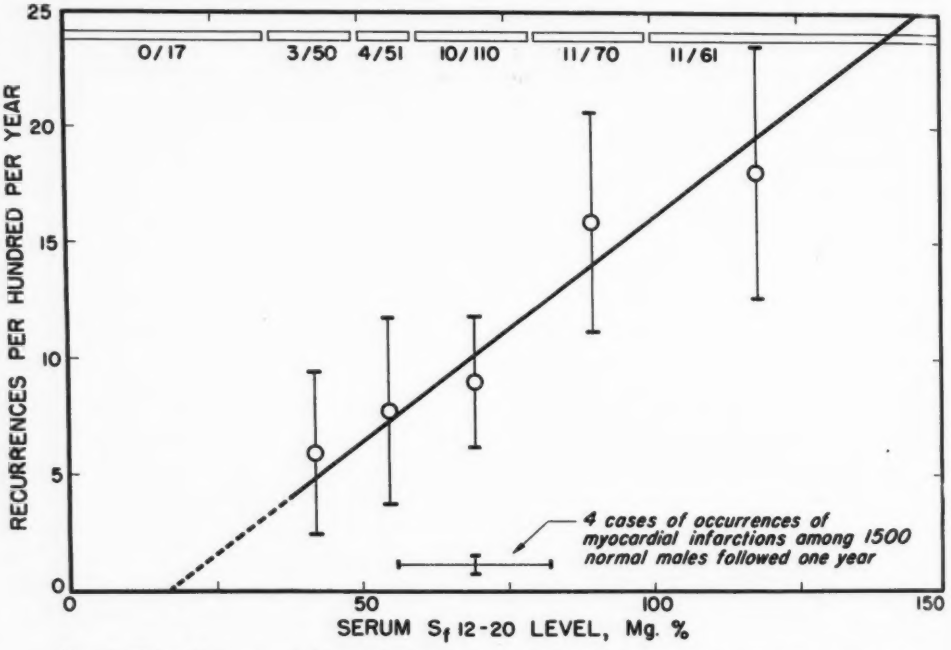

FIG. 3. Shows the per cent chance of recurrence of myocardial infarction in patients with coronary artery disease as a function of S_f 12–20 lipoprotein level. It is based upon 39 recurrent myocardial infarctions in one year follow-up of 359 patients with known coronary artery disease. The class intervals are indicated for each calculation made of the recurrences and the number of patients with myocardial infarction that have been studied. The present best estimate for the position of the similar function for the occurrence of myocardial infarction, de novo, in normals is also shown.

It is seen that the levels are much higher in those not surviving the episode of myocardial infarction than in those who do survive. A significance test splitting the survivors and nonsurvivors at 80 mg. per 100 cc. gives a probability of 1 in 10,000 that the observed difference is not significant. Since the two groups were comparable in age, sex, and previous history, it is justifiable to regard the only difference as the lipoprotein level difference. It will be noted that among the survivors the average level is lower than for those myocardial infarction survivors studied at least six weeks beyond the acute episode (see fig. 13). We have frequently observed rises in level in a given patient after the acute phase of a myocardial infarct is past. This probably indicates that in infarction survivors there is a lability of lipid metabolism incidental to the acute insult, which in itself may have increased the chance of survival. From studies reported elsewhere,[6] it seems possible that this lipoprotein alteration may be related to increased release of heparin or a heparin-like substance. The higher levels observed in the nonsurvivors suggest the possibility that the more extensive atherosclerogenesis and/or accumulated

atheroma most likely present in this group has unfavorably influenced the prognosis.

The data on recurrences of myocardial infarction and the prognosis during the acute phase of an infarct indicate that the over-all outlook for the patient above 80 mg. per 100 cc. S_f 12–20 lipoproteins is quite poor when he develops coronary disease. It is therefore of real importance to evaluate the possibility of giving such patients some protection against their intense atherosclerotic activity, which we have considered possible by means of reducing the S_f 12–20 lipoprotein level via a reduction of the burden of dietary fat.

Our previous and continuing studies of controlled experimental groups have shown that it is possible in most humans to reduce the S_f 12–20 and the S_f 20–100 classes of lipoproteins by restricting the total dietary fat and cholesterol intake.[2, 3] We are fully cognizant of the evidence that fat and cholesterol are synthesized in the body, but this is in no way inconsistent with the observed fact that a partial reduction in S_f 12–20 and S_f 20–100 lipoprotein levels is achieved by a reduction of total fat intake. The first analysis of a dietary follow-up among patients with coronary artery disease can now be made. Of especial pertinence is a comparison of those patients with high S_f 12–20 lipoprotein levels who have experienced recurrent infarction during the period of follow-up with a group of patients of comparable levels who have not shown recurrence during the one year of follow-up. The only therapeutic measure directed toward reduction of lipoprotein levels was the advice and directions for a low fat–low cholesterol diet. A diet of less than 50 Gm. of fat and 200 mg. of cholesterol per day was advised, but it is evident that one cannot assess how rigorously a given patient adhered to this regimen. Therefore, the objective criterion of serial lipoprotein determination was used solely as the measure of dietary response.

Fifty-six cases of myocardial infarction with very high levels (above 80 mg. per 100 cc. S_f 12–20) followed with serial lipoprotein determinations for one year are considered. Out of this group there were 16 recurrent myocardial infarctions during the one year follow-up. Since the patient's statement as to adherence to a low fat diet is untrustworthy, we have eliminated such information from the analysis. A segregation of this group is presented only on the basis of the reduction or nonreduction of the lipoprotein level for the period of follow-up. In this sample it appears there is a differential favoring *nonrecurrence* of myocardial infarction at any relatively reduced level of S_f 12–20 lipoproteins achieved by diet, but for the purpose of demonstrating a significant effect we have divided the group on the basis of whether the level has been reduced and maintained below 70 mg. per 100 cc. or whether the level has remained above 80 mg. per 100 cc. The following fourfold table (table 4) sharply defines the observed result.

Application of a test of significance has shown a probability of one chance in 100 that

TABLE 3.—*S_f 12–20 Lipoprotein Level in 49 Patients during First Week after Acute Myocardial Infarction*

Level of S_f 12–20 Lipoproteins	Cases Studied during Acute Phase	
	Survived	Died of Infarct
Above 95 mg. per 100 cc.	0	6
Above 80 mg. per 100 cc.	0	13
Above 60 mg. per 100 cc.	6	20
Below 60 mg. per 100 cc.	17	6
Total	23	26

TABLE 4.—*Relation of Recurring Myocardial Infarction and S_f 12–20 Lipoproteins Sustained at or Reduced from High Levels*

	Recurrence Group	Nonrecurrence Group	Totals
Cases starting and maintaining average level above 80 mg. per 100 cc. S_f 12–20	17	26	43
Cases starting above 80 mg. per 100 cc. but reducing and maintaining level below 70	0	14	14
Totals	17	40	57

this segregation is not significant. Therefore the observation that the recurrences have been in the group that maintained a high level is highly significant, and we can conclude that dietary reduction of S_f 12–20 level has given significant protection against recurrence of myocardial infarction during this year period of observation. In table 5 are the initial S_f 12–20 level and the average level for the period of follow-up for each of the groups of table 4.

The various groups turn out to be closely matched for initial S_f 12–20 levels. The only exception is the nonrecurrence group which started above 80 mg. per 100 cc. and reduced to an average level below 70 mg. per 100 cc.

TABLE 5.—*Initial S_f 12–20 Level and Average Level during Period of Follow-up for Two Groups Shown in Table 4*

	Recurrence Group			Nonrecurrence Group		
	Initial Level	Average Level	% Reduction	Initial Level	Average Level	% Reduction
Cases starting and maintaining average level above 80 mg. per 100 cc.	112	105	6	116	99	15
Cases starting above 80 mg. per 100 cc. but reducing and maintaining level below 70	—	—	—	104	57	45

Here the slightly lower initial level (by 8 mg. per 100 cc.) is the result of the lack of a single matched case at 200 mg. per 100 cc. in this group, compared with the other two groups. In the light of our recent findings that the S_f 20–100 class of lipoproteins are also highly associated with atherosclerosis, and that they are more easily influenced by the restriction of fat, it is likely that reduction in S_f 20–100 may also have afforded part of the protection observed.

DISCUSSION AND SUMMARY

1. A variety of serum lipid disturbances experimentally induced in the rabbit, some of which are associated with the development of atherosclerosis, have been analyzed. The S_f 10–30 class of lipoproteins, which develops in the rabbit in certain of these experimental procedures, is highly associated with and universally concurrent with the development of atherosclerosis, independent of the type of metabolic disturbance experimentally induced. The normally occurring lipoproteins (S_f 10 and less), even when elevated experimentally, show no significant positive association with atherosclerosis. Certain other cholesterol bearing lipoproteins (S_f 100 and higher) are either not associated with atherosclerosis or are inversely associated with atherosclerosis.

2. In the rabbit, total serum cholesterol levels, considering as a group all the types of induced lipid metabolic disturbances, are either unrelated to atherosclerosis, or may be inversely associated with atherosclerosis. Only under the special condition where the major fraction of the cholesterol is in the S_f 10–30 class of lipoproteins does total serum cholesterol correlate well, positively, with atherosclerosis.

3. An estimate of the quantitative association of the S_f 12–20, S_f 20–35, S_f 35–100 lipoprotein classes and of total serum cholesterol with atherosclerogenesis in the human has been made, studying each on the same serum sample from a given individual. Patients with coronary artery disease have served as a criterion group for the atherosclerotics. Throughout the entire age range evaluated, from 41 to 60 years, the S_f 12–20 lipoprotein levels show at least a twofold, and up to a possibly tenfold, higher relationship with atherosclerosis than does the total serum cholesterol. The S_f 20–100 lipoproteins (containing the S_f 20–35 class plus the S_f 35–100 class) also show a correspondingly higher relationship with atherosclerosis than does the total serum cholesterol. The S_f 12–20 lipoproteins and the S_f 35–100 lipoproteins are partially intercorrelated; but each shows, in addition, strong independent associations with atherosclerosis. The S_f 20–35 lipoproteins show a lesser association with atherosclerosis than either of the other classes, and, further, much of the association that is present depends upon partial correlation of the S_f 20–35 lipoprotein with either S_f 12–20 or S_f 35–100 or with both.

The S_f 12–20 and S_f 35–100 lipoproteins show strong association with atherosclerosis,

regardless of age or total serum cholesterol level. Thus, even for individuals with the same total serum cholesterol, be it low, moderate, or high, there is strong ability of the S_f 12–20 and S_f 35–100 lipoproteins to segregate atherosclerotics from normals.

Total serum cholesterol shows a much lower ability to segregate atherosclerotics from normals in the 41 to 50 year age group than the S_f 12–20 and S_f 35–100 lipoproteins. In the age group 51 to 60, while the lipoproteins maintain their strong association with atherosclerosis, there is only a borderline ability, if any, of the serum cholesterol to segregate atherosclerotics from normals.

4. What little association total serum cholesterol does have with atherosclerosis is wholly due to its partial correlation with the S_f 12–20 and S_f 20–100 lipoproteins, which are strongly associated with atherosclerosis. In essence, this means that approximately 10 per cent of the serum cholesterol is important for atherosclerosis (namely, the fraction in the S_f 12–20 and S_f 20–100 lipoproteins), while the remaining bulk, approximately 90 per cent, of the cholesterol is unassociated with atherosclerosis. As a result of the fact that the vast bulk of the serum cholesterol is in nonatherogenic lipoproteins, the measurement of total serum cholesterol in an over-all way, does more to obscure the atherosclerotic potentialities of an individual than to clarify them.

5. Even marked hypercholesteremia is not uniformly associated with atherosclerosis. The groups manifesting advanced atherosclerosis (including patients with coronary disease or xanthoma tuberosum) are strikingly segregated from equivalently hypercholesteremic individuals without manifest atherosclerosis by the S_f 12–20 and S_f 35–100 lipoprotein measurements.

6. The crude estimate of the factors which segregate atherosclerotics from normals, based upon biserial correlation, indicates that the combined S_f 12–20 and S_f 35–100 lipoproteins account for at least 35 per cent of the total etiologic factors. When the impurity of the normal population (i.e., admixture with atherosclerotics), the fallibility of diagnosis in the criterion group with coronary disease, the focal factors in atheroma formation, the difference between accumulated atherosclerosis and atherosclerotic activity, and the biologic and technical variation of measurement are all taken into consideration, the combined S_f 12–20 and S_f 35–100 lipoproteins will account for at least 75 to 80 per cent of the total variation between atherosclerotics and normals, and may very well account for the entire difference.

7. Follow-up studies have shown that early recurrence of myocardial infarction in patients with coronary disease is positively and highly related to the S_f 12–20 lipoprotein levels. The recurrence rate of myocardial infarction is approximately 20 per cent per year for those patients with S_f 12–20 levels of 100 mg. per 100 cc., whereas the recurrence rate is approximately 6 per cent for those patients with S_f 12–20 levels of 50 mg. per 100 cc. It may be that when the combined S_f 12–20 and S_f 35–100 levels are evaluated, the relationship of recurrence with lipoprotein level may become stronger.

8. The occurrence of myocardial infarction, de novo, in normals is positively related to elevation in S_f 12–20 lipoprotein levels.

9. The depression of high S_f 12–20 levels by dietary restriction of fat and cholesterol has been shown to decrease significantly the chance of recurrence of myocardial infarction in patients with established coronary artery disease. At this time a significant statement on the point of dietary protection can be made on a follow-up of high-level patients with coronary disease (above 80 mg. per cent S_f 12–20) only because their recurrence rate has provided significant data in a short period.

10. The demonstration that the S_f 35–100 lipoproteins, in addition to the S_f 12–20 lipoproteins, are associated with atherosclerosis is of especial significance with respect to the ingestion of fat. This class of lipoproteins, the S_f 35–100 class, may be raised acutely in a high proportion of humans following ingestion of fat. In patients with a severe degree of the lipid metabolic derangement which leads to "abnormal" lipoprotein patterns, this S_f 35–100 class of molecules is sustained even postabsorptively. It appears, since we have already demonstrated that a dietary lowering of the

S_f 12–20 lipoproteins has an ameliorative effect on coronary disease (based upon atherosclerosis), that dietary fat restriction is equally important, by way of depressing the S_f 35–100 level, in the effort to control atherosclerosis.

11. The rating of a patient with respect to atherosclerogenic potentialities is best achieved by a measure of the levels of S_f 12–20 lipoprotein and S_f 35–100 lipoproteins. Of the two measures, the S_f 12–20 level is the more stable, not being acutely influenced by diet. The S_f 35–100 level, even though more variable acutely with diet, is nevertheless highly associated with atherosclerosis and provides valuable additional assessment with regard to atherosclerogenesis. Thus we may regard the S_f 12–100 lipoproteins as the "atherosclerogenic band" of the serum lipoproteins. The exact assessment of relative atherogenicity of each subsegment within this region is not now possible, so that, for the present, classification is made without weighting within this region.

Acknowledgments

As part of a long-term evaluation of the prognostic significance of lipoproteins in atherosclerosis, several groups are participating in the provision and evaluation of clinical subjects, in both normal and disease categories. The results of this follow-up will be published jointly by the cooperating groups. Some of the clinical material reported on in this paper has been furnished by such groups, for whose cooperation the authors are grateful. The groups involved are The Framingham Heart Project of the United States Public Health Service (Thomas Dawber, M.D.), The Los Angeles Civil Service Commission (Edward Phillips, M.D.), The Eastman Kodak Corporation (David Fassett, M.D.), The Pan American Airlines (Frederick Leeds, M.D.), The United Airlines (A. C. Ladd, M.D.), the Permanente Hospital (Morris Collen, M.D., and David DeKruif, M.D.), The Fort Miley Veterans Hospital (Gerald Whipple, M.D., and Gordon Hein, M.D.), The Medical Department of San Quentin Prison (Leo Stanley, M.D., and Justin Fuller, M.D.). Individual physicians furnishing material are Hyman Engelberg, M.D., Francis Chamberlain, M.D., Harry Akesson, M.D., Frank Anker, M D., Norman Leet, M.D., William Donald, M.D., Alexander Yankley, M.D., Mary Lou Eilert, M.D., Dale Groom, M.D., Henry Kempe, M.D., and John Sampson, M.D.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Wallace, C. S.: Bacterial Endocarditis with Emphasis on the Escherichia-Aerobacter Group as a Causative Agent: Report of a Fatal Case. Ann. Int. Med. **34:** 1463 (June), 1951.

Following removal of an abscessed kidney resulting from infection with *Aerobacter aerogenes*, a 22 year old female continued to manifest evidences of sepsis. A blood culture during this period demonstrated the presence of the same organism. Sensitization studies indicated that the organism was highly resistant to penicillin, streptomycin and bacitracin but sensitive to polymixin. The patient died from acute myocardial failure, 48 hours after therapy with an impure preparation of polymixin was begun. At autopsy, there were engrafted on a normal mitral valve, several vegetations from which *Aerobacter aerogenes* could be cultured. In addition, the spleen was infarcted, and a severe acute toxic myocarditis was present. It is believed that cure would have resulted from polymixin therapy if myocardial failure had not supervened.

WENDKOS

Nesvadba, P.: Experiences in the Treatment of Subacute Enterococcus Endocarditis. Cardiologia **18:** 121, 1951.

The author reports two cases of subacute bacterial endocarditis due to enterococcus infection superimposed on rheumatic heart disease. Both cases had been treated previously with high doses of penicillin, which not only proved ineffective but apparently produced increased resistance to the antibiotic, as evidenced by sensitivity tests. In both instances combined treatment with penicillin (120 and 551 million units respectively) and streptomycin (28 Gm. and 114 Gm. respectively) led to a complete remission, observed in the first case over a period of 20 months and in the second for over four months. The most peculiar circumstance in the two observations was the favorable response to treatment in vivo, while complete resistance of the micro-organism to both antibiotics was found in vitro.

PICK

CONGENITAL ANOMALIES

Potts, W. J., and Riker, W. L.: Surgical Treatment of Pulmonary Stenosis with Intact Interventricular Septum. Arch. Surg. **62:** 776 (June), 1951.

Pure pulmonary stenosis is defined as pulmonary valvular stenosis with an intact interventricular septum. The stenosis is not in the infundibular region and there is no over-riding of the aorta as seen in the tetralogy of Fallot. The degree of fusion of the pulmonary cusps determines the severity of the symptoms. Often a patent foramen ovale is associated with this defect; its size determines the degree of cyanosis. Poststenotic dilatation of the pulmonary artery is always present.

A shunt operation, such as is employed in cases of tetralogy of Fallot, is apt to lead to excessive strain on the right heart. Instead, the suggested surgical approach is a direct one on the valve itself. The authors use a right transventricular approach as described by Sellors and Brock. They have devised an expanding valvulotome and an expanding dilator for incision and dilatation of the stenosed pulmonary valve from inside. Their surgical technic is described in detail.

They have operated on 13 patients ranging in age from 23 days to 17 years. One death occurred on the

operating table due to cardiac arrest. Otherwise, there were no serious complications. The results from surgery are reported as excellent in 11 patients and fair in one.

Prior to surgery, all cases had slight to tremendous right ventricular enlargement and a systolic pulmonic murmur. Cyanosis was present in 12, and enlargement of the liver was noted in 10 subjects. Cardiac catheterization revealed high right ventricular and a low pulmonary pressure. Angiocardiography was not routinely used.

FROBESE

Adams, H. D.: Congenital Arteriovenous and Cirsoid Aneurysms. Surg., Gynec. & Obst. **92:** 693 (June), 1951.

There are two distinct types of arteriovenous aneurysms: the acquired or traumatic, and the congenital. The more localized congenital lesions are termed "congenital arteriovenous aneurysms" and the more diffuse hemangioma-like lesions are called "cirsoid aneurysms." The findings in 22 such cases are presented.

The congenital lesions most often have many arteriovenous communications of small caliber. They may be present for years without symptoms, and then they may progressively enlarge and show all of the classic findings. Locally, a palpable tumor, possibly with visible venous pulsation, is noted. A palpable thrill and an audible bruit continuous throughout the cardiac cycle are diagnostic. Other findings are elevated venous pressure, elevated oxygen saturation of venous blood, and eventually cardiac enlargement and cardiac decompensation. Angiography may aid in diagnosis.

The treatment of choice is surgical removal of the lesion. When the involvement is so extensive as to affect an entire limb with multiple communications, little short of amputation can be done. In localized lesions, a single stage excision is accomplished. In deeper, larger lesions, a two-stage operation is used. The first stage consists of proximal ligation of the major arterial trunk to the area. At the second stage, the lesion is resected. These anomalies may also occur in the viscera, such as stomach, duodenum, pancreas, spleen, lung and kidney. Resection of the organ involved is indicated. In the surgical attack on aneurysms, the major blood supply should be under control at all times and this should be in an area away from the aneurysm.

FROBESE

Thurnher, B., and Weissel, W.: Ascending Aorta Forming the Left Heart Border in Morbus Caeruleus. Cardiologia **18:** 45, 1951.

The authors present radiologic data of four cases of cyanotic congenital heart disease in which an unusual anomaly, levoposition of the ascending aorta, could be demonstrated by angiocardiography. Suggestive roentgenologic signs in an ordinary postero-anterior view are: a heart shadow of normal size; prominence of the shadow of the superior vena cava or innominate vein on the right side; an abnormal bulging at the usual level of the auricular appendage on the left side; absence of the aortic knob, but a normal aortic impression of the barium-filled esophagus. The clinical, radiologic and angiocardiographic findings of the four cases are discussed in detail, and an analysis of various positional anomalies of the aortic arch is presented. From the embryologic standpoint, levoposition of the ascending aorta represents one of the instances of abnormal rotation of the truncus arteriosus, namely, incomplete rotation in inverse direction.

PICK

CONGESTIVE HEART FAILURE

Moody, R. W.: Maintenance Dose and Toxicity of Digitoxin. Ann. Int. Med. **34:** 1349 (June), 1951.

The maintenance dose of digitoxin is between 0.05 mg. and 0.2 mg. per day. Only rarely is less or more required. Patients frequently become toxic on a dosage of 0.2 mg. daily. Digitoxin possesses the advantage of standardization by weight and of nearly complete absorption of an oral dose. Digitoxin possesses the disadvantage of very slow dissipation. Toxic effects may persist as long as a week after discontinuance. Age, sex and weight have very little, if any, effect on the maintenance dose of digitoxin. Patients weighing over 180 pounds may require slightly larger dosage than those weighing less. It appears probable that, with digitoxin, toxic signs frequently appear before symptoms.

WENDKOS

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Basset, A.: Shock in Myocardial Infarction. Arch. mal. du coeur **44:** 426 (May), 1951.

The author produced an experimental infarct on the anterior surface of an exposed and denervated turtle heart. This led to complete auricular and ventricular standstill, which was verified by electrocardiograms. Following resection of the infarcted ventricle auricular activity reappeared. This would suggest some toxic depressing action effected by the infarcted muscle upon the rest of the myocardium. This hypothesis was further supported by a second experiment in which an excised turtle heart stopped beating when placed in a fluid containing extracts of cauterized skeletal muscle, and resumed its contractions following perfusion with Ringer's solution.

According to the author, the experimental data presented can be applied to human pathology. Cardiovascular collapse, frequently observed following myocardial infarction, can be explained by the action upon the heart of toxic products originating in its infarcted part. Thus, myocardial infarction

would represent a condition leading to traumatic shock which may or may not be reversible.

PICK

MacDonald, G. E., and Bentley, W. B. A.: Acute Myocardial Infarction. A Ten-Year Study. New England J. Med. **244:** 743 (May 17), 1951.

The study is based upon the findings in a series of 100 cases of acute myocardial infarction in which postmortem examinations were performed. Patients' ages ranged from 40 to 87 years, the majority in the 60 to 64 year age group. The clinical diagnosis was made correctly without the aid of the electrocardiogram in 69 per cent of the cases. In only 11 per cent of the cases did the electrocardiograms fail to show changes suggestive or characteristic of myocardial infarction. The distribution of areas of infarction was as follows: anterior, 68 per cent; lateral, 23 per cent; posterior, 30 per cent; anterior portion of the interventricular septum, 22 per cent; posterior portion of the septum, 6 per cent; posterior aspects of the right ventricle, 1 per cent. Ventricular rupture had occurred in eight cases. In 39 patients there were 45 coronary arteries occluded by recent thrombi. When the degree of coronary arteriosclerosis was estimated for all patients, the vessels were considered normal in 2 per cent. A comparison of the clinical and pathologic estimates of the age of the infarcts, made in the 76 cases in which the data permitted such a study, showed a reasonable correlation in 92 per cent. The majority of "silent" infarcts occurred postoperatively or in patients with cerebral thrombosis, cerebral arteriosclerosis, carcinomatosis or similar conditions which may have masked the symptoms produced by the infarct.

ROSENBAUM

Morrison, L. M.: The Increased Incidence of Coronary Thrombosis in Chronic Peptic Ulcer. Rev. Gastroenterol. **18:** 313 (May), 1951.

It can be definitely stated that an increase in coronary atherosclerosis and coronary thrombosis with myocardial infarction occurs in chronic peptic ulcer. It is suggested that the mechanisms of this increased incidence may be (a) excessive, prolonged stimulation of the gastric vagal nerve supply with reflex effects on the coronary arteries; and (b) possibly the excessive, prolonged daily dietary intake of fat and cholesterol, extending over a period of years. Indirect evidence indicates that such a prolonged increase in daily dietary fat and cholesterol intake predisposes to the development of coronary atherosclerosis in susceptible individuals. An evaluation of the effects of prolonged Sippy diets and/or the use of dietary protein supplements instead of whole milk and cream feedings in peptic ulcer is merited.

BERNSTEIN

Goldstein, R., and Wolff, L.: Hemorrhagic Pericarditis in Acute Myocardial Infarction Treated with Bishydroxycoumarin. J. A. M. A. **146:** 616 (June 16), 1951.

Hemopericardium has been observed during the course of bishydroxycoumarin therapy for acute myocardial infarction. Two cases of proved and one of suspected hemopericardium are discussed. The authors state that since the preparation of the manuscript two more instances have been found in postmortem examinations. Diagnosis should be suspected in the presence of prolonged and persistent or recurrent friction rub, recurrence of cardiac pain, vascular collapse accompanied with distended neck veins, and demonstration of pericardial effusion. Hemorrhage into the pericardium in such cases is an emergency. Every physician using the drug should be aware of the possibility. The treatment should include withdrawal of bishydroxycoumarin, the intravenous injection of vitamin K (preferably vitamin K_1 oxide), and repeated transfusion of blood or plasma until the prothrombin time reaches normal levels. If cardiac tamponade develops, a pericardial tap should be done.

KITCHELL

Garn, S. M., Gertler, M. M., Levine, S. A., and White, P. D.: Body Weight versus Weight Standards in Coronary Artery Disease and a Healthy Group. Ann. Int. Med. **34:** 1416 (June), 1951.

This report presents data on the body weight in men who have experienced myocardial infarction prior to the age of 40, in comparison with the body weight of a comparable group of healthy males; both are given in comparison with a set of standard weights corrected for age and height. While the healthy, active males showed age-group deviations from +4 to +22 pounds above the norms, the men who had experienced myocardial infarction showed age group deviations of from −.8 to +28 pounds. Both groups were statistically "overweight" as compared to the standards. However, when the two groups were compared to each other in terms of the deviations from the norms, no real difference was seen. The age-group deviations showed the same pattern in both groups; the deviations from the normal standards were greatest at the younger age levels.

WENDKOS

Gertler, M. M., Garn, S. M., and Levine, S. A.: Serum Uric Acid in Relation to Age and Physique in Health and in Coronary Heart Disease. Ann. Int. Med. **34:** 1421 (June), 1951.

Serum uric acid determinations were made on three groups of individuals. These groups were (a) 146 healthy working men, (b) 92 men who had experienced myocardial infarction prior to the age of 40, and (c) 97 healthy men who were "matched" to the men of the coronary disease group. The levels of the serum uric acid were 4.64 ±.76, 4.85 ±.74

and 5.13 ±1.10 for the control group, matched control group, and the coronary disease group, respectively. Twenty-four per cent in the coronary disease group and 6 per cent in both the control group and the matched control group possess levels of serum uric acid of 6 mg. per cent or over. There is no age rise in serum uric acid from the third to the fifth decades in either the coronary disease group or the control group. A physique difference of serum uric acid levels is apparent. The dominant endomorphs in both the control group and coronary disease group exceed all other physiques in the content of uric acid in the serum; the dominant ectomorphs have the smallest amount of uric acid in the serum. In coronary artery disease, the uric acid physique difference is accentuated. The rise in serum uric acid in the presence of coronary heart disease is 15.19 per cent in the endomorphs, 8.49 per cent in the mesomorphs, and 3.22 per cent in the ectomorphs. There is no relationship between the ingested purines and the level of serum uric acid. The ratio, uric acid times cholesterol-phospholipids, is considered to be of more value in assessing the biochemical background of the coronary disease state than is either of the constituents considered separately.

WENDKOS

Swan, D. M., and McGowan, J. M.: Shoulder-Hand Syndrome following Myocardial Infarction. J. A. M. A. **146:** 774 (June 30), 1951.

Reflex dystrophy of the upper extremity (the shoulder-hand syndrome) occurs in approximately 10 to 20 per cent of cases of myocardial infarction with varying degrees of disability. In the past various treatments have been recommended for this condition with indifferent results. The authors report three cases treated by stellate block with procaine hydrochloride by means of the anterior approach. This fairly simple method has been consistently successful in the authors' cases.

KITCHELL

Mussaffia, A.: The Relationship between Angina Pectoris and Myocardial Ischemia Due to Coronary Insufficiency. Cardiologia **18:** 65, 1951.

The author describes nine cases with typical anginal pain on exertion whose electrocardiograms remained normal at rest as well as following exercise during a long period of observation. After several years, while the clinical syndrome (intensity and duration of pain attacks) remained unchanged, the electrocardiogram became abnormal in four cases revealing on exercise transitory signs of ischemia. The five other cases, after a longer or shorter period, developed typical clinical and electrocardiographic signs of myocardial infarction.

The author discusses the pathogenesis of angina pectoris. The cases presented and other observations in the literature suggest that myocardial ischemia by itself is neither necessary nor sufficient to produce anginal pain. In some cases coronary sclerosis, by "irritating" sensory fibers in the vessels, may evoke typical pain without electrocardiographic signs of coronary insufficiency, which develop only at a later stage, with progression of the vascular lesion.

PICK

ELECTROCARDIOGRAPHY

Donzelot, E., Metianu, C., Durand, M., Cherchi, A., and Vlad, P.: The Electrocardiogram in Tetralogy of Fallot (a Study of 100 Cases). Arch. mal. du coeur **44:** 97 (Feb.), 1951.

A study of electrocardiograms obtained on 100 cases of Fallot's tetralogy, all submitted to surgery and 10 with autopsy, revealed the following data: the P wave was tall in 80 per cent, of variable contour and never widened. In the limb leads, QRS invariably showed marked right axis shift, and the angle between the axis of QRS and the axis of the T wave was always more than 60 degrees. In the precordial leads, the usual type was Rs or R in V_1 (83 per cent) and rS, QS or qrS in V_6 (68 per cent). The R-S ratio in V_1 was ≥ 1 in 90 per cent of the cases and, in $V_6 < 1$ in 69 per cent. In 84 per cent the intrinsicoid deflection in V_1 occurred 0.03 second after the onset of QRS, or later. Vertical electrical position was rare (3 per cent) and horizontal position frequent (68 per cent). From this study the authors consider the most reliable electrocardiographic signs of right ventricular hypertrophy to be: onset of the intrinsicoid deflection in V_1, simultaneously with or later than the same deflection in V_6; a right axis shift of more than 100 degrees; an R-S ratio in V_1 of 1 or greater than 1.

PICK

Mikulicich, G.: Electrocardiographic Changes in Experimental Anaphylactic Reactions. J. Allergy **22:** 249 (May), 1951.

In rabbits, a shock dose of antigen given two weeks after a sensitizing dose, produced marked electrocardiographic changes even when the animals did not show a general reaction. The changes started from one-half to three minutes after the termination of the injection and consisted first of bradycardia, then of tachycardia interrupted by extrasystoles. $S\text{-}T_1$ was depressed with elevation of $S\text{-}T_3$. QRS_1 became higher in voltage and wider. QRS_3 showed a marked deepening of the S waves, giving a left axis deviation. T_1 was inverted and T_3 upright. Ventricular extrasystoles, auricular fibrillation and bundle branch block were also noted. All these changes lasted about 15 minutes. If the rabbit died, the usual changes of the "dying heart" were noted. Rabbits sensitized by passive transfer and then injected with the horse serum antigen showed similar electrocardiographic changes. Two rabbits showed electrocardiographic changes with the sensitizing dose alone.

The author believes that the changes noted are a partial expression of smooth muscle spasm of coronary vessels, anoxemia of heart muscle due to contraction of lung arterioles, and permeability changes of the tissues.

BERNSTEIN

Van Dooren, F., Boyadjian, N., Bastenier, N., Collin, J., and Bierlaire, J.: The Diagnostic Value of the Angle α of the Electrical Axis. Arch. d. mal. du coeur **44:** 407 (May), 1951.

The authors determined the angle of the axis of the P, QRS and T deflections in 2965 electrocardiograms of normal persons and patients with various types of heart disease. Both in normal and abnormal cases they found a great variability of the angle; the average normal values were +55 degrees for the P axis, +39.3 degrees for QRS axis and +33.6 degrees for the T axis. A deviation of all three axes to the left was found in obese and hypertensive individuals, and to the right in pulmonary disease patients. In mitral stenosis, the QRS axis points to the right and the axes of P and T are markedly deviated to the left. A less constant and more complex abnormal relationship of the three axes is found in coronary disease and in intraventricular conduction defects. The authors concluded that the determination of the angle α does not add valuable information to that obtained from the classic three lead electrocardiogram.

PICK

Stevenson, I., Duncan, C. H., and Ripley, H. S.: Variations in the Electrocardiogram Changes in Emotional State. Geriatrics **6:** 164 (May–June), 1951.

The authors studied a group of 35 patients, 18 men and 17 women, approximately half of whom were over 45 years of age. The majority had complaints referable to the cardiovascular system, some originating in structural heart disease, others in purely functional disturbances. The principal emotional state observed was anxiety. Changes in the electrocardiographic pattern were found most commonly in the T waves, and somewhat less frequently in the P waves and S-T segments. Slight changes in the electrical axis of the heart were occasionally seen, and in one case there was a considerable change in the electrical axis related to shift in the position of the diaphragm. No abnormalities of the duration of the complexes or the intervals between them were observed.

The effect of maximal inspiration on the T waves was studied in a number of cases. Of 15 patients thus studied, in eight a maximal inspiration did not in any way reproduce the changes observed during emotional disturbance. In the remaining seven the T waves changed in the direction of the changes during the emotional disturbance. Changes in rhythm, extrasystoles, paroxysmal auricular tachycardia and paroxysmal auricular fibrillation were observed in relation to emotional disturbances. Patients with structural heart disease were found somewhat more susceptible to the occurrence of disturbances of rhythm than those with structurally normal hearts. In general there was a close relationship between the occurrence of emotional disturbances (judged by the observations of the physician and the statements of the patient) and the occurrence of electrocardiographic changes, particularly of heart rate. In five of the 19 patients whose response to exercise was tested, the rate after exercise did not reach that coincident to anxiety during the interview. In 14 patients the rate immediately after exercise was comparable to that attained during the periods of emotional disturbance.

The authors suggest that sympathetic stimulation rather than cardiac anoxia is responsible for the changes in the T waves observed during emotional disturbances. It was apparent that during the discussion of such life situations and to a greater extent during the situations themselves, the patients reacted with a symbolic, but exaggerated and disproportionate mobilization of their circulation.

BERNSTEIN

Myre, S. L., and Fuller, B. F.: Left Bundle Branch Block with Spontaneous Remission after at Least Three Years. Ann. Int. Med. **34:** 1497 (June), 1951.

A routine electrocardiogram, made in the course of a complete study of a 50 year old male with a toxic labyrinthitis, demonstrated the presence of a left bundle branch block. The remainder of the examination, including chest roentgenogram and the usual routine laboratory procedures, was entirely negative. There were no symptoms to suggest the presence of a coronary or myocardial deficit. During the ensuing two years, he returned for follow up electrocardiographic study at six month intervals and at such times the findings were unchanged. Six years later, when he was 56, he returned for another follow-up examination and at this time the electrocardiogram was entirely normal and all other findings were negative. Regardless of the electrocardiographic findings, he has always remained free of any cardiac symptoms and there has not developed any indication of a cardiovascular handicap. The cause for the spontaneous disappearance of the bundle branch block is not immediately evident. The experience with this case corroborates the view that bundle branch block, in the absence of other expressions of organic heart disease, must not necessarily be construed to be of serious prognostic import.

WENDKOS

Dreyfuss, F., and Diengott, D.: The Value of the Measurement of the Q-T Interval in a Series of

Clinical Electrocardiograms. Cardiologia **18:** 211, 1951.

The Q-T interval was measured in six leads of 303 electrocardiograms. The upper normal value of 0.420 was adopted for a corrected Q-T. In 144 electrocardiograms, the corrected Q-T interval was found to exceed 0.420. Fifty-eight of these were without other electrocardiographic abnormalities. The highest average (0.431) among cardiac disorders was found for the group of electrocardiograms taken in hypertensive cardiovascular disease. The average values for the group of rheumatic heart disease and arteriosclerotic heart disease were lower. Several severely ill cases of liver disease, kidney disease and Vitamin B complex deficiency states showed prolonged $Q\text{-}T_c$ intervals. Changes were also noted in several infections, metabolic disturbances and in coronary insufficiency. The Q-T interval seems to be a sensitive indicator of the presence of cardiac impairment in a number of pathologic states. The inclusion of the determination of the corrected Q-T interval into the routine of clinical electrocardiography is suggested.

BERNSTEIN

Braun, K., Fryd, C. H., and Liban, E.: Electrocardiographic Changes in Hypopotassemia Complicated by Pericarditis. Cardiologia **18:** 244, 1951.

A case of hypopotassemia complicated by pericarditis is reported. Serial electrocardiograms showed the changes characteristic of hypopotassemia as well as those caused by the pericarditis. It was also found that, during the acute stage of the pericarditis, the subepicardial injury pattern of the pericarditis was predominant over the injury pattern caused by the hypopotassemia.

BERNSTEIN

ENDOCRINE EFFECTS ON CIRCULATION

Sato, H.: Studies on the Cardiac Rhythm of the Dog in Experimental Hyper- and Hypothyroidism. Tohoku J. Exper. Med. **53:** 317 (March 25), 1951.

The cardiac rhythms of dogs, during the phases of respiration in particular, were studied by "cardiotachograph" in experimentally induced hyper- and hypothyroidism. In hyperthyroidism, besides tachycardias, marked decrease and finally complete disappearance of respiratory arrhythmias were noticed. These can be looked upon as characteristics in hyperthyroidism.

In hypothyroidism, on the contrary, bradycardia was accompanied by exaggerated respiratory arrhythmias. A distinct correlation between respiratory arrhythmia and pulse rate was noticed throughout the experimental conditions. These changes in respiratory arrhythmia were found to be due mainly to changes in the expiratory pulse intervals. The inspiratory pulse intervals, on the other hand, were modified but little.

BERNSTEIN

Remington, J. W.: Circulatory Factors in Adrenal Crisis in the Dog. Am. J. Physiol. **165:** 306 (May), 1951.

Arterial pressure, heart rate, cardiac index and resistance were followed simultaneously in adrenalectomized dogs in (a) terminal adrenal insufficiency, (b) acute crisis produced by minor amounts of trauma or hemorrhage in dogs still apparently healthy and (c) acute crisis following a bilateral adrenal removal at a single operation. In all, the development of circulatory crisis was initiated by a sharp fall in resistance and in blood pressure. Unlike the normovolemic intact dog, a rise in cardiac index did not follow this fall in resistance. The available reserve blood volume, as measured by the response to Isuprel, was subnormal before the resistance decline and fell progressively during the crisis. The pressor response to epinephrine was probably not normal before crisis, but did not diminish obviously until shortly before death. Pressor responses to more weakly active pressor agents were progressively reduced in early crisis. The pressor response to afferent nerve stimulation was lost early, although respiratory response was still present. An exaggerated, or prominent because unopposed, vagal reflex was common. All animals showed a marked sensitivity to anesthesia. Heart size was not only small but fixed as the filling time was altered. It is argued that a reasonable explanation of these findings may lie in a metabolic failure of the nervous system, one characteristic of which is a loss of sympathetic function.

OPPENHEIMER

Axelrod, A. R., and Berman, L.: The Bone Marrow in Hyperthyroidism and Hypothroidism. Blood **6:** 436 (May), 1951.

The authors review the literature and analyze the blood and bone marrow findings in 26 patients with hyperthyroidism and nine patients with myxedema. In hyperthyroidism anemia is not a frequent finding and when present may be of any type. Erythrocytosis is fairly common. The changes in the peripheral blood are not necessarily related to the severity or the duration of the hyperthyroidism. The available information concerning the bone marrow in hyperthyroidism is summarized. There is an extension of the red marrow into the shafts of long bones with diminution or absence of fat and with osteoporosis. Hypertrophy of the marrow organ may occur with or without anemia and with or without increased cellularity in the normal sites of hematopoiesis. There is a tendency for relative myeloid leukocytic hyperplasia with, in some instances, a relative increase in mature granulocytes. Megakaryocytes are of normal or increased frequency, independent of

anemia and not reflected by alteration of the peripheral platelet count. Relative lymphocytosis is the most constant significant change in the marrow pattern in patients with hyperthyroidism. The hematologic changes seen in some cases suggest a hemolytic disturbance.

In hypothyroidism anemia is a common but not constant finding. In uncomplicated cases the typical anemia is macrocytic hypochromic and of moderate severity. The bone marrow in hypothyroidism is hypoplastic but there is not always a reciprocal increase in fat. Hyperemic tissue and acellular material may occupy the bulk of the space in marrows which do not have increased fat contents. The hypoplasia affects all of the myeloid systems about equally.

The authors attribute the marrow changes in both hypo- and hyperthyroidism to a direct effect of the thyroid gland dysfunction, but point out that the changes of lymphoid tissue and lymphocytosis in the bone marrow of patients with hyperthyroidism may be due to secondary effects of adrenal origin.

BEIZER

Braid, F.: Hypothyroidism in Childhood. Brit. M. J. 4716: 1169 (May 26), 1951.

The author classifies hypothyroidism of childhood into three prognostic groups. The first and largest group consists of the congenital hypothyroids, in which the signs first appear during infancy. Prognosis in this group is intimately related to early diagnosis, and to early and adequate treatment. Growth is normal in this group, and only occasionally a cerebral defect is revealed by thyroid medication. Treatment requires detailed supervision over years, and often produces a worthwhile member of society. In group 2, the signs of hypothyroidism appear after some acute infectious illness. The outlook here is good, and normal physical development may be expected. The later the onset of symptoms, the better the outlook. The time at which treatment is commenced after the onset is of less importance than among group 1. Group 3 consists of constitutional degenerates with hypothryoidism. They have slow physical and mental development before thyroid deficiency is noticed. In these, goiter may develop early or during adolescence. Prognosis among these is not good. Epilepsy and spastic palsy may complicate the picture. This group appears to be lessening of late.

TANDOWSKY

HYPERTENSION

Drury, D. R., Flasher, J., Gordon, D. B., and Dorough, M. E.: Renin Substrate and Renal Hypertension Including One-Stage Method for Evisceration in the Rabbit. Am. J. Physiol. **164:** 630 (March), 1951.

Tachyphylaxis to renin in rabbits occurs more quickly after hepatectomy or abdominal evisceration than in normal animals. This refractoriness lasts at least four hours once it is established in the hepatectomized animal, and seems to be permanent. These facts support the view that renin substrate is produced only by the liver. The authors conclude that the renin-angiotonin theory of renal hypertension is untenable because renal hypertension persists after removal of the liver and destruction of "floating" substrate by excess of administered renin. These findings apply to both early and late hypertension.

OPPENHEIMER

Friedman, S. M., Friedman, C. L., and Nakashima, M.: Sustained Hypertension following the Administration of Desoxycorticosterone Acetate. J. Exper. Med. **93:** 361 (April), 1951.

A large group of rats received moderate amounts of desoxycorticosterone acetate and saline intermittently for a few weeks. Then these uninephrectomized animals were observed for an additional period of 54 weeks. Approximately one-third of the rats so treated developed a sustained, permanent hypertension after treatment had been stopped. No significant differences were noted in the blood urea levels or blood volumes between the hypertensive and nonhypertensive animals. Plasma potassium, which was significantly depressed during acute treatment with desoxycorticosterone acetate (DCA), became normal in both groups after treatment was completed. Although the kidneys of the treated animals showed some pathologic changes consistent with previous DCA activity, no differences were noted between the group of animals that remained consistently hypertensive and those which were normotensive.

This sustained hypertension was not due to any anatomic fault in the kidneys and in one sense is not primarily renal in origin. The authors postulate that the adrenal cortex normally secretes a pressor agent which is eliminated in some way by the kidneys. In this view desoxycorticosterone acetate is considered only as a representative of the natural pressor agent.

WAIFE

Locket, S., Swann, P. G., and Grieve, W. S. M.: Methonium Compounds in the Treatment of Hypertension. Brit. M. J. **4710:** 778 (April 14), 1951.

This report is based on the use of pentamethonium bromide and hexamethonium bromide in 34 patients with essential hypertension, with continued observation on 38 additional patients during the same period. Their ages ranged from 39 to 70. The average age of females was 53, and males 59. Two weeks of initial observation preceding routine treatment were used as a control for the final results. It was found that in every case, methonium compounds accomplished no more blood pressure reduction than the rest in bed. Oral administration of these compounds

in outpatients also failed to lower blood pressure. One patient died as the result of this therapy, and three probable cases of bromide intoxication resulted. In an addendum the authors present 12 additional patients who received methonium compounds with the same results.

TANDOWSKY

Sennett, L. W., Perlstein, M. A., Andelman, M. B., Barnett, H. E., and Josephy, H.: Hypertension in Poliomyelitis with Respiratory Paralysis. Pediatrics **7:** 529 (April), 1951.

Sustained hypertension complicating an acute protracted poliomyelitis of 24 weeks duration in a 16 year old boy is reported. On admission, the blood pressure was 130/82. It was not until five weeks later that the blood pressure was elevated and ranged from 170/100 to 190/120. The blood pressure rose to 260/140 with the onset of convulsions on the day of death. At autopsy the spinal cord had numerous astroglia scars and the medulla oblongata and the mesencephalon showed the findings characteristic of acute poliomyelitis. The nucleus ambiguus and the reticular formation were the areas of the brain stem most affected. The kidneys revealed marked subacute pyelonephritis with calcific deposits in the tubules. There was no evidence of renal disease or of hypertension prior to the present illness. With the discovery of the hypertension, the urine was found to contain both granular and hyaline casts with a constant trace of albumin. The concentration and dilution tests were normal. The paraaminohippurate clearance showed decreased effective renal blood flow, but the glomerular filtration rate was normal and the filtration fraction increased. It was thought that increased sympathetic outflow with diffuse vasospasm of the efferent arterioles was responsible for the increased filtration fraction and may have been a sustaining mechanism in the hypertension. The authors also suggest that the lesions in the brain stem and the lateral horns of the spinal cord played a contributing role in either the etiology or the maintainance of the hypertension. However, whether the irritable vasomotor apparatus or the renal disease was responsible for the hypertension is not known.

MARGOLIES

Krane, S. M., and Perera, G. A.: Hypertension in Age Groups. Ann. Int. Med. **34:** 1017 (April), 1951.

A group of patients who died at the age of 60, with hypertension not known before the age of 55, was compared with another group of younger established hypertensives who died from some cause other than the usual complications of hypertensive vascular disease. The incidence and degree of renal arteriosclerosis were considerably greater among the younger patients, while among the older patients they approximated those observed in elderly subjects with a normal blood pressure. Although a mild form of essential hypertension cannot be excluded in this group of elderly patients, it is suggested that many instances of hypertension in later life may be due to some basis other than that producing the usual picture of hypertensive vascular disease.

WENDKOS

Stamler, J., Hwang, W., and Kuramoto, K.: Renal Clearances of Sodium and Chloride in Goldblatt Hypertensive Dogs. Am. J. Physiol. **165:** 328 (May), 1951.

This study was undertaken to determine whether a disturbance in sodium and chloride excretion could be demonstrated in Goldblatt hypertensive dogs by renal clearance methods. No differences were demonstrated between normotensive and hypertensive dogs under varying sodium chloride load. Both showed increased renal plasma flow and glomerular filtration rate when sodium chloride solution was infused. There was no characteristic renal pattern of strong electrolyte excretion in hypertension.

OPPENHEIMER

Blacket, R. B., and Sellers, A. L.: The Effect of Removing the Constriction of the Renal Artery in Acute and Chronic Hypertension in the Rabbit. Clin. Sc. **10:** 177 (May), 1951.

Rabbits were made hypertensive by removing one kidney and later constricting the renal artery of the remaining kidney. The constriction was removed in one group 2 to 17 days following its application, and in a second group 6 to 24 weeks after application. In the acute group, blood pressures usually returned to preoperative levels within 24 hours. In the chronic group, the time required was generally several days, though in two cases normotensive levels were reached within 24 hours.

The authors believe that not only the initiation but the maintenance of hypertension in the rabbit depends on renal artery constriction. Initially hypertension is probably due to the release of renin by the ischemic kidney. The decline of chronic hypertension when the renal artery is unclamped may be explained in one of two ways. First, there may be retention in the body of a substance normally excreted by the kidney, the accumulation of which might lead to hypertension. After removal of the clamp, this substance may be gradually excreted. Second, it has been suggested that a depressor substance, possibly secreted by the kidney, may have its rate of production lessened by renal ischemia and increased by removal of the clamp.

ENSELBERG

Dumoulin, J. G.: Tetraethylammonium Bromide in Toxemia of Pregnancy. Lancet **260:** 1257 (June 9), 1951.

These experiments show that the response to in-

travenous tetraethylammonium bromide varies and is of little diagnostic use, and that TEAB is of doubtful therapuetic value. In the severe cases there is a tendency toward lack of response to TEAB. The reason for the variability of the response to TEAB is unknown. Fear may cause an increased secretion of adrenaline, which may nullify the action of TEAB; pregnant patients tend to be apprehensive. The autonomic blocking effect of TEAB may be incomplete. TEAB in the dosage used (500 mg. intravenously) can be toxic, and in larger doses, lethal. Investigators who used TEAB in labor reported strong and sustained uterine contractions, but such were not observed in any of the antenatal cases reported here. It is felt that TEAB is of very limited practical value in the study and treatment of pregnancy toxemia.

BERNSTEIN

Gordon, D. M.: Routine Examination of the Ocular Fundi as an Aid in Management of Toxemias of Pregnancy. J. A. M. A. **146:** 810 (June 30), 1951.

The author discusses examination of the fundi in two groups of pregnant women. First, those where pregnancy is complicated by hypertensive phenomena; second, those cases where previous hypertension is in danger of becoming more complicated by pregnancy. In the discussion it is pointed out that all the eyeground studies in toxemias of pregnancy which have been carefully done, indicate that such observations serve as a great aid in management of these cases. Sometimes the decision to interfere with pregnancy must be made on the basis of this type of examination. The author feels it is important that the examination should be made after the pupils have been dilated with either 2.5 per cent Neosynephrine hydrochloride or 3 per cent paredrine hydrobromide. It is important to follow out carefully all the four major branches of the vessels and one should be sure that the light is adequate for good viewing. The author feels that in those cases in which the fetus is viable and the eyeground signs clearly show evidence of toxemia little is to be gained by waiting. Here interference with surgical delivery is indicated, as fetal death may occur very suddenly.

KITCHELL

PATHOLOGIC PHYSIOLOGY

Shenkin, H. A., Cabieses, F., vanden Noordt, G., Sayers, P., and Cooperman, R.: The Hemodynamic Effect of Unilateral Carotid Ligation on the Cerebral Circulation of Man. J. Neurosurg. **8:** 38 (Jan.), 1951.

The authors investigated the cerebral circulatory hemodynamics of four patients who had intracranial arterial aneurysms and were treated with unilateral ligation of common carotid artery. Studies were made of the cerebral blood flow, carbon dioxide and oxygen contents of arterial and both jugular vein blood, and the mean systemic arterial blood pressure, before and 10 minutes after carotid ligation. The cerebral oxygen consumption and cerebrovascular resistance were calculated from these findings.

In all four cases the cerebrovascular resistance increased following carotid ligation. The average increase was 47 per cent. Also the mean systemic arterial blood pressure increased in all cases; the average increase amounted to 20 per cent. There were no significant changes in cerebral blood flow and cerebral oxygen consumption in three of the four cases. However, in the fourth patient, the cerebral blood flow and cerebral oxygen consumption fell to very low levels as the cerebrovascular resistance rose abnormally high. This patient became comatose and hemiplegic in eight minutes. The authors concluded that in all cases the resistance across the circle of Willis after common carotid ligation was considerable and it was particularly high in the patient who became hemiplegic. Thus, the authors feel that the desired reduction of vascular pressure head in treating intracranial aneurysms by ligation may give rise to neurologic sequelae if it lowers the cerebral blood flow proportionately.

FROBESE

Griffin, G. D. J., Wood, E. H., and Essex, H. E.: Variability of Direct Fick Values and Validity of Right Atrial Blood Samples in Determining Cardiac Output of Anesthetized Dogs. Am. J. Physiol. **164:** 583 (March), 1951.

The authors suggest that even in dogs deeply anesthetized for 1.5 hours or more the cardiac output is constantly shifting. There was no greater variability in mixed venous blood and cardiac output values determined from successive samples from the pulmonary artery and right atrium than from successive samples withdrawn from the pulmonary artery. It appears that, with care in positioning of catheters, right atrial blood samples from anesthetized dogs may not differ significantly from a true mixed venous blood sample and presumably could be used with validity in calculating heart output by the direct Fick method in these animals.

OPPENHEIMER

Malamani, V., Bobba, P., and Baldrighi, C.: The Functional Pressure Changes of the Right Atrium and Ventricle. Proc. XII Meet. Ital. Soc. Cardiol. Folia cardiol. **9:** 229 (March), 1951.

The authors studied the behavior of the intracardiac pressures under physiologic conditions, such as deep breathing, cough, abdominal contractions, various decubitus, and after exertion. The study was made in 14 normal adults by right heart catheterization, using a Hamilton manometer.

It was found that intracardiac pressures vary especially in deep inspiration. In this phase, auricular pressure dropped to −5 mm. Hg during systole and −7 mm. Hg during diastole; ventricular pres-

sure dropped to +20 mm. Hg during systole and −6 mm. Hg during diastole. Cough caused an increase of pressures to +60 mm. Hg for the auricle and +80 mm. Hg for the ventricle. During the Valsalva test, the pressures were positive: auricular pressures reached +10 and +14, ventricular pressure, +70 and +100, during diastole and systole, respectively. Intermediate values were found during abdominal contraction.

LUISADA

Polzien, P., and Reinold, F.: Esophageal Pulsations and their Meaning. Ztschr. f. Kreislaufforsch. **40:** 225 (April), 1951.

The authors describe a method for sphygmographic registration of the volume pulse of the aortic arch and of the left ventricle by means of a closed rubber tube induced into the esophagus to various levels. In a young healthy individual, synchronization of the curve obtained at the level of the aorta with the carotid pulse permitted the calculation of the pulse velocity (317 cm. per second) between the two vessels. The complicated curve, obtained at ventricular levels, was analyzed with the help of a simultaneously recorded electrocardiogram. By timing of the various waves in the ventriculogram, the authors arrived at the following values: at a cycle length of 0.714 second (corresponding to a rate of 84 per minute) the time of isometric contraction was 0.073 second and the ejection time 0.238 second.

PICK

Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V.: The Effect of Intravenous Infusions of Physiologic Saline Solution on the Pulmonary Arterial and Pulmonary Capillary Pressure in Man. J. Clin. Investigation **30:** 345 (April), 1951.

Certain physiologic determinations were made before, during, and after the intravenous administration of saline solution at a rate of from 77 to 146 cc. per minute in amounts of 950 to 1000 cc. In all of the 12 adult men studied there was a rise in pulmonary arterial pressure within one or two minutes of the start of the infusion. The mean pulmonary arterial pressure rose from 12 mm. Hg to 20 mm. Within an hour after the infusion the pulmonary arterial pressure returned to or toward normal. A similar increase in pulmonary capillary pressure was noted following the rapid infusion of saline. The total blood volume rose about 14 per cent. The pulmonary blood volume showed an average increase of 12 per cent, but with a range of from −6 to +45 per cent of the control value. Five of eight subjects showed a decrease in the vital capacity at the end of the infusion. In six cases the cardiac output increased significantly after the infusion, while in another six the cardiac output remained within normal limits. The pulse rate and direct arterial pressure measurements were essentially unchanged.

The authors conclude that the changes induced by a rapid saline infusion can be explained best on the basis of abrupt, but not disproportionate, increase in the amount of blood contained in the relatively indistensible pulmonary circuit.

WAIFE

Griffin, G. D. J., Essex, H. E., and Mann, F. C.: Experimental Evidence Concerning Death from Small Pulmonary Emboli. Surg., Gynec. & Obst. **92:** 313 (April), 1951.

The authors reviewed the literature with regard to the question of whether or not death could occur as a result of embolism in one or a few small pulmonary arteries. Some of the workers were of the opinion that this was not possible in man except in those cases in which severe cardiac or pulmonary disease already existed. In the experimental animal it was not demonstrated to the satisfaction of all investigators that death of the subject from pulmonary embolism was caused by other than purely mechanical factors.

ABRAMSON

Reese, H. L., Darrow, R. P., and Cullen, M. L.: Calf Muscle Blood Flow, before and after Operation and during Various Normal and Pathologic States. Surg., Gynec. & Obst. **92:** 751 (June), 1951.

The authors studied the calf muscle circulation of man by determining the rate of disappearance of radioactive sodium injected into the gastrocnemius muscle. A mean rate was obtained by studying 44 patients with clinically normal peripheral vascular systems. They found that exercise increased the sodium clearance above the resting value and also that the sodium clearance was reduced below resting values in the antagonistic muscles.

Eight cases of arteriosclerosis obliterans were investigated and it was found that the mean circulatory clearance was lower than normal. However, there was considerable individual overlapping into the normal range. From this latter fact, it was concluded that the method had little value as an individual diagnostic measure in arteriosclerosis obliterans.

The sodium clearance rate of 16 patients with phlebothrombosis was measured. There was much individual variation, but the mean rate was the same as the preoperative rate. Therefore, the results indicated that effective calf muscle circulation was not reduced by phlebothrombosis. Four of these cases had bilateral superficial femoral vein ligation and were studied. No change in the normal rate was noted.

Forty-two cases were studied before and after operation and no significant change in the mean sodium clearance was noted.

Thoracolumbar sympathectomy was found to increase the sodium clearance rate in four cases. However, of four patients studied before and after lum-

bar sympathectomy, two had an increased rate and two had a decreased rate.

The sodium clearance method accurately reflects muscle blood flow changes, but its usefulness as a clinical test for predicting or diagnosing postoperative phlebothrombosis is limited because of physiologic variations.

FROBESE

Post, R. S.: Decrease of Cardiac Output by Acute Pericardial Effusion and Its Effect of Renal Hemodynamics and Electrolyte Excretion. Am. J. Physiol. **165:** 278 (May), 1951.

Acute pericardial effusion in dogs increases central resistance to venous return and hence causes a rise in venous pressure. Heart output decreases although the fall in systemic arterial pressure is not so great, because of a sustaining vasoconstriction. Renal vasoconstriction is less than in other areas, since the fraction of the cardiac output flowing through the kidney is increased. Total peripheral resistance increases more than renal resistance. Glomerular filtration rate and renal blood flow are both decreased. The smaller filtration rate means that a smaller amount of sodium is presented to the tubules, reabsorption is increased and excretion of sodium decreased. Venous pressure rise was too small to be important in sodium retention. Potassium was retained, but to a lesser degree than sodium.

OPPENHEIMER

Denolin, H., and Lequime, J.: Alterations of the Circulation in Chronic Cor Pulmonale. Arch. mal du coeur **44:** 391 (May), 1951.

The authors report respiratory and cardiodynamic studies in 12 patients with chronic pulmonary disease and arterial O_2 desaturation of 67 to 90 per cent. Ten cases were cyanotic and showed a significant dilatation of the pulmonary artery at x-ray examination and right axis shift in the electrocardiogram. Four cases had signs of heart failure. Autopsies on two of the latter cases revealed right heart dilatation and atheromatosis of the pulmonary vessels.

The lowered arterial oxygen content present in all cases dropped further during an exercise test. However, the oxygen utilization coefficient (O_2 consumption per hour)/(ventilation per hour) was elevated during exercise, as it is in normals. This indicates that in chronic cor pulmonale pulmonary ventilation is more depressed than oxygen consumption. In the majority of the cases cardiac output was high, whether or not there was heart failure, and the pressure in the cavities of the right heart was elevated. In accordance with views expressed in the literature the authors conclude that impaired alveolar ventilation is the principal pathologic factor responsible for the various clinical manifestations of chronic cor pulmonale.

PICK

Dieckmann, W. J., Smitter, R. C., Horner, E. N., Pottinger, R. E., Ryukiewicz, L., and Lundquist, R.: Etiology of Pre-Eclampsia-Eclampsia. III. The Effect of Oral Ingestion of Sodium Chloride and Sodium Bicarbonate by Patients with Toxemia of Pregnancy. Am. J. Obst. & Gynec. **61:** 1100 (May), 1951.

The authors classify pregnant patients as having pre-eclampsia and/or eclampsia when there is (1) rapid or excessive weight gain, (2) edema after bed rest, (3) a marked negative water balance and decrease in weight following delivery. The presence of hypertension and/or proteinuria is not essential so long as evidence of abnormal electrolyte and water retention is observed.

Previous studies by this group had demonstrated that intravenous sodium salts administered to patients with true pre-eclamptic manifestations were harmful. In non-toxemic patients with edema and weight gain, the infusion was innocuous. In the present study, 104 patients with clinical evidence of toxemia were given sodium chloride or lactate tablets, alternating with placebo therapy, for periods each of one or more weeks.

Of the entire group, 70 per cent of the patients failed to show any difference in their response to sodium salts compared to placebos. In some patients, presumably true pre-eclamptics, there was a definite increase in weight gain, edema, blood pressure and proteinuria. It is suggested that the patients who were unaffected by the administration of sodium salts do not have true pre-eclampsia and the term "pseudopre-eclampsia" has been applied to this group.

SHUMAN

Hurst, W. W., and McPhail, F. L.: Toleration of a High Water Intake by Patients with High-Grade Mitral Stenosis in the Last Trimester of Pregnancy. Am. J. Obst. & Gynec. **61:** 1001 (May), 1951.

In this series of 16 patients with serious heart disease, the effect of the administration of large amounts of fluids was observed. There were 18 pregnancies in this group, all associated with congestive heart failure due to mitral stenosis, with aortic valve lesions combined in five. Each of these patients was studied for an average period of 12 days, during which the fluid intake ranged from 3000 to 6000 cc. per day. Saline-containing infusions were used only where emesis or duodenal drainage necessitated replacement of sodium and/or chloride. Whenever blood, plasma or saline were administered, large amounts of water by mouth or isotonic dextrose were given. There was one maternal death due to subacute bacterial endocarditis.

The authors emphasize the need for adequate amounts of plain water which will maintain true water balance without causing heart failure or pulmonary edema. The volume of water recommended

depends upon the antecedent water deficit, the vaporization losses, and the requirements of the kidney for urine formation; it is given by mouth or, if necessary, may be given by vein as 5 per cent dextrose in water. The diet should provide a moderate restriction of sodium with a slight excess of acid ash.

SHUMAN

Newman, M. M., Bay, E. B., and Adams, W. E.: Ballistocardiography in Experimental Mitral Insufficiency. Am. J. Physiol. **165:** 497 (June), 1951.

Pure mitral insufficiency was studied by right heart catheterization and low frequency ballistocardiograms. All animals showed a rise in right ventricular and pulmonary artery pressure. There was no change in oxygen consumption, arteriovenous oxygen difference, cardiac output, stroke volume or ballistocardiogram. Section of the anterior mitral leaflet via the atrium was the method used to produce regurgitation.

OPPENHEIMER

Moyer, J. H., and Handley, C. A.: The Problem of Renal Vascular Shunts. Am. J. Physiol. **165:** 548 (June), 1951.

Renal clearance studies were carried out before and following sciatic nerve stimulation on nine dogs in order to evaluate the significance, if any, of renal vascular shunts. No evidence was found to support the hypothesis that renal vascular shunts cause acute anuria.

OPPENHEIMER

Harris, A. S., Estandia, A., and Tillotson, R. F.: Ventricular Ectopic Rhythms and Ventricular Fibrillation following Cardiac Sympathectomy and Coronary Occlusion. Am. J. Physiol. **165:** 505 (June), 1951.

Abrupt coronary artery occlusion in dogs with open chest is followed by a 10 minute period (phase I) of ectopic discharges of increasing frequency which either pass through a maximum and then decrease or end in fibrillation. A two stage occlusion avoids the danger of fibrillation in this phase. During the next four and one-half to eight hours the ectopic frequency is no more than 5 per minute (phase II) in those animals which survive. Following this there is a rapid increase in ectopic frequency (phase III) which reaches a maximum in 10 to 20 hrs. after the artery has been tied. This ectopic activity usually lasts two to four days. Experiments were devised to obtain evidence concerning the effects of upper thoracic sympathectomy upon the occurrence of ectopic ventricular complexes during each of these three phases. The authors, as a result of their experiments, came to the point of view that "multiple excitatory factors contribute to the production of ectopic impulses following coronary occlusion during all three phases and that sympathetic nerve excitation is one of these factors." This sympathetic nerve factor is of minor or moderate importance in the first phase, the main factor although not a powerful one in the second phase, and a small factor in the last phase. Differences in the amounts of other excitatory influence in the three phases may account for the varying importance of spontaneous sympathetic impulses. Only after Pentothal anesthesia is there enough ectopic ventricular activity to be studied adequately in the second phase. These bouts of activity after Pentothal did not occur when upper thoracic sympathectomy preceded coronary occlusion.

OPPENHEIMER

Berlin, N. I., Bowles, D. F., Hyde, G. M., Parsons, R. J., Samson, P. C., and Port, S.: The Blood Volume and Blood Turnover in Thoracic Surgery as Determined by P^{32} Labelled Red Blood Cells. Surg., Gynec. & Obst. **92:** 712 (June), 1951.

By the use of P^{32} labeled red blood cells, the blood volume changes were studied in 27 patients that had thoracic operations. The study included calculations of blood volume, total red cell volume and plasma volume two to six days prior to surgery and two to six days after surgery in each case. The object was to determine losses from both the operative procedure and bleeding into the wound and body cavities postoperatively.

Most of these operations were carried out in subjects with pulmonary tuberculosis. The blood volume turnover or loss in first stage thoracoplasty was found to vary from 840 to 1500 cc. Second stage thoracoplasty showed a loss of 350 to 1410 cc. of blood. During pneumonectomy, the turnover varied from 1640 to 5090 cc. of blood. The volume of red blood cell loss was proportionately greater than the amount of apparent plasma loss in these cases.

The hematocrit, hemoglobin concentration and plasma protein determination did not give an accurate indication of the diminished blood volume in these cases. It was felt that the dye methods of determination of blood volume were less satisfactory than the labeled red cell methods. Blood volumes determined by the dye methods are approximately 15 per cent higher than those determined by the labeled red cell method. This is due to loss of dye into the cells of the reticuloendothelial system, loss into the lymphatic system, and the longer mixing time required with Evans blue in comparison with labeled red cells.

The magnitude of blood loss in thoracic operations makes blood volume studies with correction of existing deficits very important.

FROBESE

PATHOLOGY

Geiringer, E.: The Mural Coronary. Am. Heart J. **41:** 359 (March), 1951.

The author found that in 23 of 100 unselected

autopsies the anterior coronary artery runs for all or part of its course in the myocardium. Such arteries are referred to as "mural" coronaries. The anterior descending branch of the left coronary artery was selected because of its straight course, ease of measurement, and because atherosclerotic lesions appear in it early. In the mural coronary, the overlying myocardium may be 5 mm. or more thick, and its covering fibers run at right angles to the course of the vessel. These fibers belong to the superficial layer of the myocardium, the so-called vortex fibers. In some cases, the left anterior descending coronary artery divided near its origin into two parallel branches, one of which pursued an intramuscular course. In patients of the same age and sex, in hearts of the same weight, an epicardial left anterior descending artery of the same lumen as a corresponding mural branch tends to have a considerably thicker intima. Furthermore, atherosclerosis rarely affected the mural coronary artery although it was common in the epicardial stretches.

The author believes that the myocardial investment reinforces the muscular action of the media and minimizes the mechanical stresses of intravascular tension which are important factors in the genesis of intimal hyperplasia. The lower incidence of atheroma in the mural coronaries is related to the presence of thinner intima and undisturbed vascular supply. In view of the virtual immunity of mural coronary arteries from atheroma, the author sadly laments that human coronaries do not resemble more commonly the mural distribution of the chimpanzee or orangutan arteries, rather than that of the gorilla and gibbon. In this respect, it would seem that we "are descended from the wrong type of ape."

HELLERSTEIN

Franco, P. M.: Study of Connective Atrial Bundles under Normal and Pathologic Conditions. Arch. d. mal. du coeur **44:** 287 (April), 1951.

The author found in the course of histologic studies of the atrial myocardium of human hearts several muscular connections which, in his opinion, serve for transmission of the impulse from the sinus node to the right atrium (sinoauricular pathway), to the left atrium (interauricular pathway) and to the node of Tawara (sinonodal pathway). The interauricular pathway he identifies with the previously described bundle of Bachman and the sinonodal one with the Torus Loweri.

In two cases sclerotic lesions restricted to these connection fibers could be demonstrated microscopically. In the electrocardiogram, one case had sinus rhythm with small P waves and a normal P-R interval, the other inverted P waves in lead II and III and also a normal P-R. The author feels that vascular or ischemic processes in the atrial myocardium can produce functional disturbances "analogous to those following lesions affecting the specific tissue itself."

PICK

Fisch, C.: The Heart in Dystrophia Myotonica. Am. Heart J. **41:** 525 (April), 1951.

The author found evidence suggesting heart involvement in five of six patients suffering from typical dystrophia myotonica, a familial disorder of skeletal muscles characterized primarily by slow relaxation after contraction and atrophy. The patients were all males, whose ages ranged from 35 to 56 years. The blood pressure was in the low normal range. Symptoms referable to the cardiovascular system occurred in two of five patients. In four of the five patients with abnormal electrocardiograms it was not possible to obtain a history which would suggest that the alteration might be a result of one of the more common etiologic causes. In one case, the serologic test for syphilis was positive, but there was no clinical evidence of syphilitic heart disease. Prolongation of the P-R interval was found in three patients, left bundle branch block in one patient, auricular flutter in one patient, and low amplitude of the QRS complexes in one patient. The author collected from the literature a total of 85 patients with electrocardiographic studies. The electrocardiograms were normal in 31.7 per cent. Prolongation of the P-R interval occurred in 48.3 per cent, delayed intraventricular conduction in 11.7 per cent, and auricular flutter, auricular fibrillation and nonspecific T and S-T changes in the remainder. Although detailed anatomic studies are not available, the author believes that the high incidence of electrocardiographic changes, the uniform distribution among the various age groups, and the lack of antecedent history of one of the more common etiologic agents suggest that the alterations of the cardiovascular system are an integral part of dystrophia myotonica rather than a coincidental finding.

HELLERSTEIN

Magarey, F. R.: Pathogenesis of Mitral Stenosis. Brit. M. J. **4711:** 856, (April 21), 1951.

The author reviews the current theories regarding the pathogenesis of mitral stenosis and believes that there is ample evidence to show that progressive postrheumatic valvular thickening and the development of mitral stenosis are due at least in part to organization of repeated deposits of fibrin on the surface of the valve, and in the commissures between the cusps, and that it is not necessarily dependent upon the accepted process of postinflammatory cicatricial contraction within the substance of the valve. As evidence the author presents pathologic data which show that approximately 70 per cent of the valves studied in rheumatic heart disease contain fibrin deposits, while only 7 per cent of the nonrheumatic hearts disclosed its presence. He believes that the rheumatic healing process encouraged

the deposit of fibrin on the surface and this sequence of thrombus (fibrin) formation followed by organization may be repeated throughout life, thus explaining the slow development of mitral stenosis. His studies on partially submerged valves have shown that repeated deposition of fibrin has been responsible for the gradual burial of these structures below the surface of the cusps, and this process is likewise responsible for the "shortening" of the chordae tendineae. This study is of interest in view of the findings at operations undertaken for the direct surgical relief of mitral stenosis. The author feels that if his concept is correct, the results of surgical intervention by cutting the commissures may lead to reoccurrence and still predispose to repeated thrombus (fibrin) formation.

TANDOWSKY

Moschcowitz, E.: The Relation of Hyperplastic Arteriosclerosis to Diabetes Mellitus. Ann. Int. Med. **34:** 1137 (May), 1951.

Gross arteriosclerosis of the aorta and of the pulmonary artery are entirely independent. Gross arteriosclerosis of the pulmonary artery occurs no more frequently in diabetic patients than in controls within the same age group. This observation excludes the possibility that diabetes causes hyperplastic arteriosclerosis. The incidence of arteriosclerosis of the aorta and of the coronary artery was no higher in diabetics than in the control groups. There is a substantial increase above that consequent to senescence in the incidence of arterial lesions in the pancreas in diabetes as compared to control groups. The brunt of this increase is largely dependent on the increase of hyalinization. The increase in hyalinization is the result partly of the diabetes itself and partly of an associated hypertension. Hypertension appreciably increases the total incidence of arterial lesions in the pancreas as compared with normotension. The apparent increase of arterial changes in the pancreatic arteries in diabetes is specious and is explainable by the clinical observation that older individuals with prolonged essential hypertension are potential diabetics; therefore, the number of older diabetics in whom the hypertension precedes the diabetes is considerable. Advanced age, even without hypertension, may produce hyperglycemia and diabetes. Hyalinization and fibrosis of the islands of Langerhans occur in about one-half of the pancreases of the older diabetics, but rarely in children. These lesions are therefore not specific lesions of diabetes. The arteries of the pancreas were involved in virtually 100 per cent of cases in which island lesions were present. The island lesions are interpreted morphogenetically as a capillary sclerosis, precisely comparable to that found in alveolar capillaries of the lung, the sinusoids of the liver, and in the glomeruli in the presence of arteriosclerosis and phlebosclerosis affecting the main vessels of these organs. The capillary sclerosis is the result of either the extension of the fibrosing or hayalinizing lesion of the afferent arteriole of the island into the capillaries, or of diminution of the blood supply. The reason why island lesions do not occur more frequently in diabetes is the special pattern of blood supply in the pancreas. The cause of the hypoinsulinemia in the cases in which the islands are intact is a functional insufficiency, consequent to the impairment of the blood supply to the islands. The higher incidence of gangrene of the lower extremity as compared with nondiabetics is viwed as the result of atherosclerosis, which is the characteristic lesion of diabetes. The atherosclerosis is due to a hyperlipemia and, more particularly, hypercholesteremia. All the submitted evidence makes it fairly certain that in older individuals hyperplastic arteriosclerosis precedes but does not follow the diabetes.

WENDKOS

Biork G., and Krook, H.: Myocardial Injury at Cardiac Catheterization. Report of a Case. Acta cardiol. **6:** 101, 1951.

The authors present electrocardiograms and pressure curves obtained simultaneously during cardiac catheterization of an eight year old boy with pulmonic stenosis and patent ductus arteriosus. A transient drop of pressure in the pulmonary artery and right ventricle and a pressure rise in the right auricle occurred simultaneously with transient changes in contour of the electrocardiogram. The latter consisted in marked shortening of the P-R interval or complete disappearance of the P wave, in widening of the QRS and in marked depression of the S-T segment, without changes in rate. The authors feel that the most likely explanation of the simultaneous variations of the electrocardiogram and of the pressure values is a "functional myocardial insufficiency" related to and perhaps induced by subendocardial injury in the course of cardiac catheterization.

PICK

Müller, M.: Granulomatous Giant Cell Myocarditis. Schweiz. Ztschr. f. allg. Pathol. u. Bakteriol. **14:** 146, 1951.

The author reports postmortem findings in a 45 year old woman who had no clinical signs of heart disease and who died suddenly. The heart was enlarged due to dilatation of both ventricles and showed grossly brown atrophy and fatty degeneration. Sections taken from both ventricles, the septum and the papillary muscles showed, microscopically, numerous granulomatous foci with giant cells, but no epithelioid cells, no caseation and no microorganisms were found within the lesions. The author considers a viral infection or allergy as possible causes of the isolated myocarditis.

PICK

PHARMACOLOGY

Spies, H. W., Dowling, H. F., Lepper, M. H., Wolfe, C. K., and Caldwell, E. R., Jr.: Aureomycin in the Treatment of Bacterial Endocarditis. Arch. Int. Med. **87:** 66 (Jan.), 1951.

Nine patients with endocarditis caused by alpha and beta streptococci, pneumococci and staphylococci were treated with Aureomycin. Two patients recovered with Aureomycin therapy; one recovered after receiving combined Aureomycin and penicillin therapy, and one failed to show improvement with Aureomycin therapy but recovered when he received penicillin. Of the five patients who died, one had extensive miliary tuberculosis and the others had either ruptured valve cusps or congestive heart failure which accounted, at least in part, for the fatal outcome.

In vitro studies of the synergistic action of Aureomycin and penicillin were utilized as a guide to the treatment of one patient.

It is concluded that Aureomycin is a valuable agent in the treatment of endocarditis, either alone or in combination with penicillin.

BERNSTEIN

Bickel, G., Plattner, H., and Edelstein, H.: Complete Recovery Following Intoxication with Massive Dose of Digitalis. Arch. d. mal. du Coeur **44:** 61 (Jan.), 1951.

A 36 year old woman attempted suicide by taking 50 mg. of digitaline Nativelle. The typical clinical signs of digitalis poisoning appeared within an hour. Vomiting, hiccup, somnolence, visual disturbances, and diarrhea, lasted for eight days. The electrocardiographic tracings, taken at frequent intervals, showed an extreme variability. They consisted of auricular fibrillation, auricular flutter, SA and AV block. There were no changes of the QRS complex, while the s-t segment and the T wave showed the typical digitalis effects. The electrocardiogram returned to normal in 12 days.

LUISADA

McCall, M. L., Finch, T. V., and Taylor, H. W.: Cerebral Effect of Papaverine Hydrochloride in Toxemia of Pregnancy. Am. J. Obst. & Gynec. **61:** 393 (Feb.), 1951.

Using the nitrous oxide method of measuring cerebral blood flow, the authors studied the changes produced by the intravenous administration of papaverine in a group of seven patients with pre-eclampsia and of three with hypertensive toxemia.

A drop in blood pressure was produced in both groups by the drug. Cerebral blood flow increased in most instances, while cerebral vascular resistance decreased to a normal level. There was also a significant increase in oxygen utilization by the brain.

On the basis of the results, it was felt that papaverine was worthy of a clinical trial as an adjunct to therapy in pre-eclampsia and hypertensive toxemia of pregnancy.

ABRAMSON

Pratt, E. B., Burdick, F. D., and Goldner, M. G.: Salyrgan Diuresis in the Bile Fistula Dog. Am. J. Physiol. **164:** 639, (March), 1951.

Salyrgan administration caused an increase in urine sodium before and after bile removal. In all but one dog diuresis was produced although bile was drained to the outside. This bile when administered to intact dogs produced no increase in urine sodium excretion and no significant diuresis. The authors conclude that flow of bile from liver to intestine is not essential to organic mercurial diuresis in the dog.

OPPENHEIMER

Elkin, D. C., and Cooper, F. W.: The Effect of Vasodilator Drugs on the Circulation of the Extremities. Surgery **29:** 323 (March), 1951.

Using the rate of removal of radioactive sodium chloride from the muscle as an index of muscle blood flow, the authors studied the vasodilating properties of several drugs. Supplementing this study, blood flow determinations were made by measurement of skin surface temperatures and plethysmography.

In normal subjects, nicotinic acid, papaverine and Priscoline uniformly diminished the rate of uptake of the radioactive sodium from the muscle. The same applied to sympathectomy. Priscoline and C7337 were the only agents which elevated skin surface temperature in the digits. In the case of patients with organic obliteration of the arteries, the dilator drugs either had little effect on skin surface temperatures or the blood flow was decreased.

ABRAMSON

Perera, G. A.: Cortisone and Blood Pressure. Proc. Soc. Exper. Biol. & Med. **76:** 583 (March), 1951.

The results indicate that cortisone exerts little influence on the arterial tension of normotensive patients without renal disease treated for several months with the dosages customarily used. It is possible that larger doses or therapy continued for longer periods of time may yet be associated with hypertension similar to that seen in Cushing's syndrome.

Rises in systolic and diastolic blood pressures were obtained within a few weeks in the group with renal involvement, receiving the customary doses of cortisone. From the present study it is unknown whether the kidney damage results in a greater retention or a chemical modification of the administered cortisone or whether the response of the diseased kidney to the steroid is altered.

The author recommends that cortisone be used with greater care in patients with renal disease, particularly if there is a history of antecedent hypertension.

MNITZ

Wilson, J. L., and Quash, E. T.: Intra-arterial and Oral Priscoline. A Clinical Report. Am. J. Surg. **81:** 336 (March), 1951.

The authors studied the effect of Priscoline on 17 patients with various types of vascular disorders of the lower extremities. The medication was given orally and intra-arterially.

With intra-arterial administration of an average dose of 50 mg., the patient generally experienced an intense warmth and burning sensation in the foot which lasted for several minutes. During this time there was a moderate increase in pulse rate without subjective symptoms, but no postural hypotension was encountered. Skin temperature studies showed an elevation in the readings in some cases as early as five minutes after injection. The rise in temperature lasted as long as four hours after administration and varied from 1 to 6 F. depending upon the degree of pathologic disorder. In those patients with arteriosclerosis obliterans, the effect was not as sustained as in other groups.

Priscoline was found effective in the treatment of refractory leg ulcers, provided therapy was started prior to the onset of gangrene or established soft tissue necrosis. The drug was also of use in the relief of spasm due to many different causes. However, in severe cases with gangrene, it was not of value in effecting a spontaneous amputation of a toe or toes or a lower site for surgical amputation.

It was the authors' impression that intra-arterial administration of Priscoline supported by oral therapy might replace lumber sympathectomy in selected cases of vasospasm as well as ulceration prior to the stage of advanced necrosis.

ABRAMSON

Reedy, W. J.: Comparative Effects of Ether, Alcohol, Tetraethylammonium and Priscoline in Producing Vasodilatation in Peripheral Vascular Conditions. J. Lab. & Clin. Med. **37:** 365 (March), 1951.

The author studied the effect of various vasodilating drugs on 16 subjects suffering either from arteriosclerosis obliterans or vasospastic disorders of the extremities. Changes in the skin temperature of the digits were used as an indication of the efficacy of the medication on altering cutaneous blood flow.

The intravenous injection of ether had no consistent effect on skin temperature, while alcohol infusion produced vasodilatation in the presence of vasospasm but no increase in skin temperature in patients with arteriosclerosis obliterans. The intravenous administration of tetraethylammonium appeared to have a weak action on increasing cutaneous blood flow, while Priscoline was quite effective in this regard both in arteriosclerosis obliterans and in vasospastic disorders.

ABRAMSON

Spadolini, L.: Epinephrine as a Safety Factor against Perturbing Conditions of the Systolic Rhythm on the Amphibian Heart. Arch. di fisiol. **50:** 127 (March), 1951.

The author had previously described a special type of "tetanus" of the amphibian heart. Low concentrations of epinephrine (from 10^{-5} to 10^{-6}) were found to prevent that summation process which is obtained by means of electrical stimulation of proper frequency plus hypercalcemic Ringer's solution.

Procaine was found to have the same property as epinephrine in preventing the experimental "tetanus" and to potentiate the action of epinephrine. The author believes that the procaine acts by inhibiting the fixation of calcium ions in the colloidal systems of the muscle.

LUISADA

Hurley, L. A., Roberts, J. E., Buchanan, A. R., and Tillquist, G.: Preliminary Investigation of the Value of the Dihydrogenated Alkaloids of Ergot in the Treatment of Experimental Frostbite. Surg., Gynec. & Obst. **92:** 303 (March), 1951.

The authors studied the effect of a mixture of three dihydrogenated alkaloids of ergot upon experimental frostbite in rats. The ends of the tails were frozen by immersing them in ether which was maintained at a temperature of 15 C. with solid carbon dioxide. The application was maintained for 60 seconds. The tails were allowed to air-thaw and then treatment was begun immediately.

Statistical analysis of the results revealed that, in the group of rats receiving the dehydrogenated alkaloids of ergot, the mean tail loss was significantly less than that obtained in a control series of animals. It was felt that the improvement in the treated group was due largely to the vasodilator action of the drugs.

ABRAMSON

Paton, W. D. M.: The Paralysis of Autonomic Ganglia, with Special Reference to the Therapeutic Effects of Ganglion-Blocking Drugs. Brit. M. J. **4710:** 773 (April 14), 1951.

The author reviews the drugs which interfere with the transmission of excitation across the synapsis of the autonomic ganglions resulting in ganglionic block. The author discusses the potentialities of four of these, namely nicotine, curare, tetraethylammonium, and hexamethonium. Physiologic transmission in these ganglions with adequate production of acetylcholine is discussed with its normal excitation of the ganglionic cell.

The specific action of nicotine as an autonomic ganglionic blocking agent in pharmacologic research was briefly reviewed. Curare, although free from the stimulating action shown by nicotine, has two disadvantages: it produces neuromuscular paralysis and also causes histamine liberation, the latter

interfering with the study of blood pressure and blood flow.

The author believes that tetraethylammonium is a fairly specific ganglionic inhibitor which lacks stimulant action on ganglions, but he feels that its action is relatively transient, and that its potency is not high. Its side effects were briefly discussed, particularly in reference to its clinical application. He reviews the action of hexamethonium as a ganglionic blocking agent as proved by competition and he discusses its effect on blood pressure by the release of autonomic tone, and not by direct vascular action, or an atropine-like "adrenolytic" action. The action of ganglionic blocking agents on blood pressure is thought to be an exaggeration of the mechanisms maintaining normal blood pressure when they are weakened. Its action varies, depending upon the sensitivity of the ganglions. Its use in arterial hypertension cannot be fully explored until an analysis of its complicating postural hypotension is made. Its possible relaxation of venomotor tone is discussed as a factor in the production of postural hypotension. The spontaneous inhibitory action of hexamethonium on hydrochloric acid to a point of achlorhydria is briefly reviewed and mention is made of its possible use in accelerating the healing of peptic ulcer and the relief of pain. The author feels that the action of hexamethonium holds therapeutic promise and this, in the main, is due to its action as a ganglionic blocking agent. The use of hexamethonium as a specific tool for the analysis of autonomic activity in research is mentioned and it is hoped that further investigation of its compounds will unfold the yet unknown functions of the synapses, both central and peripheral.

TANDOWSKY

Apperly, F. L., McKeown, C. E., Young, W. B., and Strayer, F. M.: Electrical Method for the Prevention of Venous Thrombosis and Pulmonary Embolism. Am. J: Surg. **81:** 451 (April), 1951.

An apparatus is described which permits passive muscular contractions in the thigh and calf induced by a sinusoidal current from a Burdick Morse Wave generator M-210. The procedure is begun as soon after operation as possible, stimulation of the muscles being maintained for 10 to 15 minutes in each hour for several hours. In some cases a course of stimulation is given on the following two days.

ABRAMSON

Sharnoff, J. G., Carideo, H. L., and Stein, I. D.: Cortisone-Treated Scleroderma. J. A. M. A. **145:** 1230 (April 21), 1951.

Moderately advanced generalized scleroderma responded dramatically to cortisone but in a period of 10 weeks irreversible hypertension complicated by uremia caused the patient's death. Not only were severe vascular lesions noted in the kidneys (similar to those frequently found in scleroderma) but also thrombotic ischemic renal infarctions were found. These were of the type often reported in polyarteritis nodosa. Such a course of events had not been reported prior to the advent of cortisone and ACTH therapy so it is suspected that the treatment given the patient may have accelerated pathologic changes preexisting in the kidneys.

KITCHELL

Natelson, R. P.: Tuberculous Pericarditis: A Report of Three Cases Treated with Streptomycin. Ann. Int. Med. **34:** 1169 (May), 1951.

One patient, a woman known to have had pulmonary tuberculosis since the age of 17, developed, at the age of 28, progressive cardiac enlargement, increasing venous pressure, decreasing blood pressure, hepatic enlargement and progressive electrocardiographic abnormalities interpreted to be diagnostic of a pericardial lesion. At this juncture, 3 grams of streptomycin were administered daily for 3½ months. When she was next seen 8 months later, there were no findings to suggest previous pericardial involvement and the pulmonary lesion was inactive. Another patient, a female known to have had pulmonary tuberculosis since the age of 17, developed, at the age of 26, the typical findings of a calcified pericardium with constrictive phenomena. She received 1 Gm. of streptomycin daily for one month following which the systemic venous pressure returned to normal. She died suddenly, eight months after completion of streptomycin therapy, of a massive pulmonary hemorrhage. An autopsy was not performed. Another patient, a male, known to have had pulmonary tuberculosis since the age of 27, developed, at the age of 29, pain in the chest, fluoroscopic findings of a pericardial effusion, electrocardiographic changes considered to be diagnostic of a pericardial lesion, and an elevated systemic venous pressure. In a small amount of pericardial fluid, removed by paracentesis, tubercle bacilli could not be demonstrated by smear or culture. One Gm. of dihydrostreptomycin was administered intramuscularly for a period of 45 days, following which objective and subjective evidences of the pericardial lesion disappeared. One year later, when he was readmitted to the hospital because of a persistently positive sputum, there were no clinical or radioscopic evidences of previous pericardial involvement.

WENDKOS

Fowler, N. O., Westcott, R. N., Scott, R. C., and McGuire, J.: The Effect of Nor-Epinephrine upon Pulmonary Arteriolar Resistance in Man. J. Clin. Investigation **30:** 517 (May), 1951.

The infusion of *l*-norepinephrine in man leads to an elevation in pulmonary artery pressure. The authors studied 13 subjects to observe the mechanism of this effect. During *l*-norepinephrine infusion there was a statistically significant rise in pulmonary

artery pressure and rise in mean brachial artery pressure with a decrease in cardiac output in five subjects; the pressures were unchanged in five others. At the same time there was a statistically significant mean rise in pulmonary "capillary" pressure, and a significant increase in total peripheral resistance, without an increase in pulmonary arteriolar resistance. In three subjects there was a definite and marked rise in right atrial pressure.

The authors conclude that during the administration of *l*-norepinephrine the pulmonary hypertension is due to an increase in pulmonary venous pressure and not to a constriction of the pulmonary artery. Furthermore, despite the rise in right atrial pressure, arterial or capillary constriction contributes to the increase in total peripheral resistance.

WAIFE

Krehbiel, S., and Stewart, H. F.: Self-Administration of a Mercurial Diuretic. J. A. M. A. **146:** 250 (May 19), 1951.

Seventy-one ambulatory patients with cardiac disease were taught to administer their own Mercaptomerin sodium injections subcutaneously. The study extended over a period of five months. Altogether 1425 subcutaneous injections were used by these individuals. An average of two teaching sessions was required by the majority of patients to learn the procedure. In most patients, and after most injections, there were no untoward reactions. Occasionally transient local discomfort and nodule formation was noted. The reactions were not severe enought to warrant discontinuance of the program. Limitations for this method of self-medication are aversion to the idea of self-injection, mental incompetence, and physical disability. Nineteen patients who were given preliminary instructions fell into these categories, leaving 71 who participated fully. The benefit could be measured financially by the patient and in reduction of routine work at the clinic, saving the time of the medical, nursing and secretarial staffs. The authors recommend widespread adoption of self-injection technic in patients who are suited to such a program.

KITCHELL

Carroll, D.: Streptomycin in the Treatment of Tuberculous Pericarditis. Bull. Johns Hopkins Hosp. **8:** 425 (May), 1951.

The course of tuberculous pericarditis is analyzed in 71 untreated cases. Thirty-nine, or 53.5 per cent, died within two years, and 14, or 19.5 per cent, survived for five or more years. Thirty-three of the 39 fatalities had widespread tuberculosis at death. In the other six cases, the process was localized to the mediastinum and the pericardium. Nine cases died in cardiac failure.

Twenty-one patients were studied who survived for five or more years; the average follow-up period was 12.6 years. Five of this group died after the five year follow-up period, two of tuberculous pericarditis in the seventh year, two of carcinoma of the prostate, and one of carcinoma of the stomach. Three had signs and symptoms, probably secondary to the previous tuberculous pericarditis; one had had an operation for chronic constrictive pericarditis, and was now fibrillating, one had calcification of the pericardium without cardiac symptoms, and the third had evidence of pulmonary involvement.

Six cases were reported which were treated with streptomycin. Early treatment with streptomycin facilitates healing with a minimum of scarring. Because pericarditis may be the initial sign of a widespread tuberculosis and because treatment is more effective early than late, the author stresses the early treatment with streptomycin and PAS even before the diagnosis is definitely proved. He advises the use of these drugs along with prolonged bed rest postoperatively for chronic constrictive pericarditis.

MARGOLIES

PHYSIOLOGY

Laszt, L., and Müller, A.: The Pressure Curves in the Left Ventricle, Atrium and in the Ascending Aorta. Helv et. physiol. et pharmacol. acta **9:** 55 (March), 1951.

By means of multiple cannulation and using four electrical transmission manometers in the open chest dog, the authors recorded simultaneously the pressure curve in the ascending aorta, the left atrium and at various points within the left ventricle. The contour of the ventricular curve was found to depend on the type of cannula and the region of recording. When the cannula was located in the region of the conus arteriosus in the direction of the streamlines, the pressure curve had a simple bell shaped contour with a plateau, or with a single or double peak. In the aorta, two preoscillations, a systolic wave and afteroscillations were seen. The duration of the two preoscillations corresponded approximately to the duration of the isometric phase of ventricular contraction. During the time of pressure rise, the pressure values in the aorta are usually a little higher than in the ventricle and the systolic maximum is usually lower in the ventricles than in the aorta. At the time of the incisura, the ventricular pressure is always lower than the aortic pressure.

PICK

Vruner, H. D., Clark, J. K., and Barker, H. G.: An Attempt to Measure Renal Circulation Time with P^{32}. Am. J. Physiol. **164:** 618 (March), 1951.

In anesthetized, eviscerated dogs and rabbits no consistent relationships were found among (a) renal circulation times as measured simultaneously by Evans blue dye and by P^{32}, (b) arterial blood pressure, (c) renal blood flow and (d) renal vascular resistance. The return of P^{32} from the kidney following intra-arterial injection occurred as a protracted wave extending over a considerable time. This was

true of the cephalic, coronary, splenic, and femoral circulations as well.

The P^{32} circulation time method provided an objective measure of the shortest vascular route but, in common with the dye method, gave no information bearing on any identifiable physiologic factor. Injections of P^{32} into individual glomerular capsular spaces in amphibia indicated that some of the protracted return from the kidney may be due to a detour of the P^{32} into the glomerular filtrate with subsequent tubular absorption.

OPPENHEIMER

Curtis, H. J., and Travis, D. M.: Conduction in Purkinje Tissue of the Ox Heart. Am. J. Physiol. **165:** 173 (April), 1951.

The false tendons of the left ventricle of the ox heart have been used to study excitation and conduction in Purkinje tissue. These strands exhibit resting and action potentials identical qualitatively to heart muscle. Responses are "all or none," conduction velocity averages 4.2 meters per second at 37 C., and the absolute refractory period lasts for the period of depolarization. Although this tissue is made up of a large number of individual cells the authors point out that the electrical behavior indicates clearly that there is a functional protoplasmic continuity between adjacent cells, and the Purkinje tissue acts as a functional syncitium.

OPPENHEIMER

Bowen, W. J.: Phosphorylysis of Adenosine Triphosphate and Rate of Contraction of Myosin B Threads. Am. J. Physiol. **165:** 10 (April), 1951.

Phosphorylysis of adenosine triphosphate by myosin B is greatly accelerated in the presence of calcium but is unchanged by magnesium. However, the rate of shortening of myosin B threads is inhibited by calcium and accelerated by magnesium. On the basis of these results it is suggested that phosphorylysis adenosine triphosphate is not directly involved in shortening of myosin B threads.

OPPENHEIMER

RHEUMATIC FEVER

Bayliss, R. I. S., Etheridge, M. J., and Hyman, A. L.: Pulmonary Hypertension in Mitral Stenosis. Lancet, **2:** 889, (Dec.), 1950.

Right ventricular and/or pulmonary artery pressures have been correlated with clinical, radiologic and electrocardiographic findings in 22 patients with mitral stenosis. Pulmonary hypertension at rest was found in 17 patients.

Patients with severe pulmonary hypertension without peripheral venous congestion presented a recognizable syndrome characterized by predominant pulmonary symptoms and electrocardiographic evidence of right ventricular hypertrophy. Patients with lesser degrees of pulmonary hypertension did not present characteristic features, but right ventricular enlargement on fluoroscopy was a constant finding. The degree of pulmonary hypertension, however, can be determined only by direct measurement.

Right ventricular enlargement was found in all patients with pulmonary hypertension. There was no relation between the size of the left atrium and the degree of pulmonary hypertension.

On exercise a striking rise in pulmonary artery pressure occurred without a significant increase in cardiac output. The pulmonary hypertension at rest and on exercise is due to stenosis of the mitral valve and to increased pulmonary arteriolar resistance. The relative importance of these two factors is discussed.

BERNSTEIN

Abrahams, D. G., Glynn, L. E., and Loewi, G.: Heparin Tolerance in Rheumatic Fever. II. Clin. Sc. **10:** 1 (Feb.), 1951.

In a previous communication the authors reported that patients with active rheumatic fever demonstrated a resistance to the anticoagulant action of intravenously administered heparin. The present study is concerned with investigations of the mechanism of this property. In vitro studies were performed with the blood of control patients and those suffering from acute rheumatic fever. In the latter group heparin resistance was found to be due to inactivation of heparin by the blood itself. This property was present in whole blood but not in serum alone. There was no correlation between heparin resistance and antistreptolysin ('O') titer.

SAGALL

Keith, J. D., and Neill, C. A.: Rheumatic Fever Treated with Cortisone and ACTH. Canad. M. A. J. **649:** 193 (March), 1951.

The authors treated 23 cases of rheumatic fever with ACTH or cortisone. Prompt relief of fever and arthritis was noted, in most cases sedimentation rate was brought to normal in three weeks, and gallop rhythm frequently disappeared. Nodules disappeared in three cases and choreiform movements ceased in four cases. An appreciable rise in hemoglobin and hematocrit usually occurred during treatment.

Patients with chronic heart failure were not improved by therapy and failure became more marked during treatment in one case. However, two cases of acute heart failure in the first attack of rheumatic fever were quickly improved with hormone therapy.

SCHWARTZ

Salt, H. B.: Plasma and Serum Proteins in Chronic Rheumatic Diseases. Ann. Rheumat. Dis. **10:** 46 (March), 1951.

The author studied the alterations in plasma proteins in chronic rheumatic states, using the

globulin moiety. He found a hyperglobulinemia in patients with these conditions, the changes being due chiefly to increments in the euglobulin and pseudoglobulin I fractions. However, it was his belief that none of the changes was specifically related to rheumatic disease.

It was concluded that the various empiric tests which have been advocated for the laboratory study of chronic rheumatism vary in sensitivity, and hence they should be replaced by direct determinations of plasma or serum protein components.

ABRAMSON

Adams, F. H., Kelley, V. C., Dwan, P. F., and Glick, D.: Response of the Serum Hyaluronidase Inhibitor and Mucoproteins to Adrenocorticotropic Hormone in Rheumatic States. Pediatrics **7:** 472 (April), 1951.

Following a control period of one to five days, 13 patients with acute rheumatic fever and two patients with juvenile rheumatoid arthritis ranging in age from 4 to 17 years, were given 40 to 100 mg. or adrenocorticotropic hormone (ACTH) intramuscularly for approximately four weeks. During the administration of ACTH, the sedimentation rate dropped to normal and the nonspecific hyaluronidase inhibitor level also was reduced to normal in 10 to 15 days, but became subsequently subnormal in all of the cases. The decrease in the sedimentation rate and the hyaluronidase inhibitor seemed to parallel the subjective improvement of the patient. The serum mucoprotein did not return to normal until approximately three to four months of ACTH therapy. In all the cases where ACTH was stopped or the dosage reduced prior to a drop in the mucroprotein level, the disease recurred. One patient manifested a combination of diabetes mellitus and rheumatic fever. The affect of ACTH on this patient's rheumatic fever was similar to that of the others. However, the insulin requirement doubled that of the pre-ACTH period.

MARGOLIES

ROENTGENOLOGY

Miller, J. E.: Anatomy of the Heart and Great Vessels. Angiocardiographic Study. Texas State J. Med. **47:** 5 (Jan.), 1951.

It is the author's opinion that angiocardiography is the most accurate method of studying cardiovascular anatomy. Normal angiocardiographic findings in the posteroanterior projection and in the oblique positions are described. It is pointed out that angiocardiographic technic shows the pulmonary conus to be situated deep in the cardiac silhouette and never forms a portion of the left border of the heart in the posteroanterior projection. "The pulmonary artery segment" is formed frequently by the left pulmonary artery and on occasion by the main pulmonary artery. In the posteroanterior projection, the right side of the heart does not occupy the major portion of the cardiac silhouette. In the right anterior oblique projection, the left ventricle occupies a considerable portion of the cardiac silhouette anteriorly.

SCHWARTZ

SURGERY IN HEART AND VASCULAR SYSTEM

Wilcox, L. D., and Grace, A. J.: Barriers to Surgery in Mitral Stenosis. Canad. M. A. J. **64:** 218 (March), 1951.

The exact diagnosis of "tight" mitral stenosis, which alone is surgical, is not always easy. The presence of significant mitral insufficiency rules against surgery since operation is likely to be associated with some additional regurgitation. Surgery should not be considered for grossly calcified mitral valves, nor if there is evidence of active rheumatic or bacterial endocarditis or significant coexisting valvular disease.

The real surgical objective is a reduction of the blood pressure in the left auricle as measured in the operating room with a saline manometer. This objective has been attained in only a few of the reported cases.

SCHWARTZ

Leeds, S. E., Mackay, E. S., and Mooslin, K.: Production of Ventricular Fibrillation and Defibrillation in Dogs by Means of Accurately Measured Shocks across Exposed Heart. Am. J. Physiol. **165:** 179 (April), 1951.

Dogs hearts have an average resistance of 50 ohms during the passage of a current. Serial shocks of 85 to 110 volts alternating current, current 1.5 to 2.1 amperes, applied for 0.1 second were recommended for defibrillation. It was more difficult to produce fibrillation and easier to defibrillate after quinidine. When fibrillation was produced by means other than electroshock, then defibrillation was much more difficult.

OPPENHEIMER

Keown, K. K., Grove, D. D., Ruth, H. S.: Anesthesia for Commissurotomy for Mitral Stenosis. J. A. M. A. **146:** 446 (June 2), 1951.

The anesthesiologic management of 50 cases of mitral commissurotomy is presented. They are given preanesthetic preparation directed toward decreasing the irritability of the heart and lessening any factors such as nausea, coughing or straining. An hour prior to anesthesia, 1½ grains pentobarbital are given by mouth; 75 to 150 mg. Meperidine and atropine sulfate 0.60 mg. (1/100 grain) given intramuscularly. The authors stress that quiet is essential in all the procedures to prevent the patient from becoming apprehensive and to prevent tachycardia from beginning. Thirty minutes prior to induction of anesthesia a solution of 0.2 per cent procaine in 5 per cent dextrose and distilled water is adminis-

tered intravenously; 350 to 750 mg. is given before intubation is carried out. Decamethonium bromide is given in doses varying from 1 to 4 mg. intravenously until the patient has difficulty in opening and closing his eyelids. Following this thiopental sodium is given intravenously in dosages sufficient to produce hypnosis. At this time a mixture of 50 per cent nitrous oxide and 50 per cent oxygen is administered by Magill endotracheal catheter. Apnea is avoided and when indicated respiratory function is augmented to assure adequate pulmonary ventilation. Nitrous oxide and oxygen are continued until the surgeon opens the left auricular appendage when 100 per cent oxygen is administered. Procaine is continued at the same concentration of 0.2 per cent with a basic flow of 1 Gm. per hour. Thiopental sodium is added as required for basal hypnosis. The authors attempt to have the patient awake, moving and responsive at the completion of surgery.

KITCHELL

Edwards, E. A., and Crane, W.: Lumbar Sympathectomy for Arteriosclerosis of the Lower Extremities. New England J. Med. **244:** 199, 1951.

The results of sympathectomy performed in 100 patients for peripheral arteriosclerosis are reported. Preoperative studies indicated moderate or severe obliterative disease in all cases. Frank or imminent necrosis was the indication for operation in 70 patients whereas intermittent claudication was the indication in the others. The early results were poor in eight patients. Eighty-nine patients were alive 2 to 36 months after operation and in this group there was only one further amputation on the operated side. The vascular status of the foot had almost invariably continued to improve. The age, sex, level of occlusion of major arteries or degree of calcification of the arteries demonstrable radiographically could not be correlated with the outcome.

Two local factors which seemed to exert an unfavorable effect upon the outcome were deep necrosis down to bone proximal to the toes and the previous loss of the contralateral extremity. Visceral disease of such severity that the patient might be expected to succumb to the operation was another contraindication to operation. A good temperature response to preoperative paravertebral or spinal anesthesia is felt to be evidence suggesting a good result from operation but failure to respond to this test does not exclude a favorable outcome. Marked hypertension and diabetes both exerted a somewhat unfavorable effect upon the outcome. The action of sympathectomy is felt to be an increase in collateral flow; the circulation cannot be restored to normal since the flow in the aggregate of small arteries is less than normal.

ROSENBAUM

THROMBOEMBOLIC PHENOMENA

De Camp, P. T., Ward, J. A., and Ochsner, A.: Ambulatory Venous Pressure Studies in Postphlebitic and Other Disease States. Surgery **29:** 365 (March), 1951.

By placing a flexible polyethylene tube into a subcutaneous vein of the foot or lower leg, the authors were able to study the venous pressure of the limb at rest in the recumbent and erect positions, and at a "standing walk." The procedure proved to be a valuable clinical diagnostic tool as well as a method of clinical investigation. Ambulatory venous pressures assisted in determining the presence or absence of disease of the deep veins in a series of patients exhibiting chronic disorders of the leg associated with trauma, spontaneous edema, cellulitis and varicose veins.

ABRAMSON

VASCULAR DISEASE

O'Keeffe, A. F., Warren, R., and Donaldson, G. A.: Venous Circulation in Lower Extremities Following Femoral Vein Interruption. Surgery **29:** 276 (Feb.), 1951.

The effect of superficial femoral vein ligation on walking venous pressure was studied in 47 extremities in which this procedure had been carried out two to seven years before, in order to prevent pulmonary embolism. As a control group, walking venous pressures were obtained on 11 normal patients.

The method used to obtain the readings consisted of inserting a 20 gage needle into one of the saphenous veins in the calf. The needle was connected to a manometer and to an elevated reservoir of physiologic saline solution by means of rubber tubing and a Y tube. The venous pressure reading was made by eliminating the reservoir from the system and allowing the saline solution in the manometer to seek a level.

After superficial femoral vein interruption the average fall of walking venous pressure in the extremities was 23.3 cm., as compared with 25.5. cm. for the normal limb. The difference between the two groups was not considered to be significant.

It was concluded that interruption of superficial femoral veins which were normal prior to operation resulted in no demonstrable change in venous circulation.

ABRAMSON

BOOK REVIEWS

Heart Disease, Its Diagnosis and Treatment. *Emanuel Goldberger.* Philadelphia, Lea & Febiger, 1951. 651 pages, 90 figures (229 illustrations), $10.00.

Dr. Goldberger, whose previous contributions have been principally in the field of electrocardiography, has written a lucid, comprehensive, and up-to-date introduction to clinical cardiology. In type, his book more closely resembles the synopsis than it does either the discursive, personalized book or the exhaustive, documented scientific work. There is, accordingly, little that is original or novel in the book, and its virtues over other books of its kind in this field lie in its succinct, simple style, and its orderly, abundantly catalogued form. For this reason it will probably have its greatest usefulness for the medical student and the physician who has had little or no experience in the diagnosis and management of heart disease.

The content of the book is accurate, responsible and conforms with generally accepted practices and ideas. There are many generalizations, dogmatisms and simplifications. Perhaps this was necessary for a book which is designed to be an introduction to clinical cardiology. However, the easy explanations for the mechanisms of heart failure in hyperthyroidism, anemia, and pulmonary emphysema, for example, will be disturbing to those who are acquainted with the actual complexity of the pathogenesis of these syndromes. The relatively lengthy discussion of "psychotherapy" of neurocirculatory asthenia is astonishingly glib and superficial, reflecting none of the recent progress in the technic of mature, responsible and sensitive care of milder emotional disorders. On the other hand the sections on fluoroscopic examination of the heart, congenital heart disease, and heart disease in pregnancy are particularly adequate, and superior to similar discussions in other books of this type. The book is remarkably up-to-date, including discussions of ion-exchange resins, Tromexan, procaine amide, oximetry, ACTH and cortisone therapy of acute rheumatic fever, ballistocardiography, and cardiac catheterization (where it is stated that the mixed venous blood sample should be obtained from the right auricle instead of from the pulmonary artery). Useful up-to-date bibliographies are appended to each chapter.

The author's judgment on certain subjects still perhaps sub judice may be of interest to readers of this review. He adopts a middle position in the controversy of the relative roles of "forward" and "backward" mechanisms in the pathogenesis of congestive heart failure; he believes lumbar sympathetic block to be of little usefulness in the treatment of acute arterial embolism; he believes hyperthyroidism itself rarely, if ever, causes heart failure; he is unimpressed by the incidence of embolism following regularization of auricular fibrillation; he believes that the average patient with acute myocardial infarction can be ambulated after two weeks of bed rest; he considers Herxheimer reactions to be sufficiently likely complications of the penicillin treatment of cardiovascular syphilis to warrant two months of prior bismuth therapy.

Perhaps the most interesting aspect of this book is that although it is written by an expert in electrocardiography, less space is devoted to the electrocardiogram than in any other book of its size in this field. An introduction and discussion of the abnormal electrocardiogram covers only 14 of the 650 pages, and even under myocardial infarction the electrocardiogram receives only three additional pages. With the many new technics and instruments in the field of electrocardiography it is useful to be reminded by an expert in the field that the electrocardiogram occupies a relatively small part in the whole field of clinical cardiology.

ROBERT P. GRANT

Hypertension: A Symposium. *E. T. Bell, ed.* Minneapolis, University of Minnesota Press, 1951. 573 pages, 116 illustrations, 90 tables, $7.50.

This volume records the proceedings of a symposium on hypertension held at the University of Minnesota, September, 1950, in honor of Professors E. T. Bell, B. J. Clawson and G. E. Fahr. Thirty papers by 24 international authorities, together with the related questions and discussion, as well as a bibliography for each paper, have been integrated by Dr. Bell into a contemporary source book on hypertension.

Discussions include the following: (1) the usefulness of experimental hypertension in the study of mechanisms by which arterial pressure can be increased and lowered; (2) the pathologic anatomy as seen in renal biopsy and necropsy material; (3) the influence upon pathogenesis of heredity, vascular hyper-reactivity, life stress in various cultures, emotional attitudes, and dietary factors such as a high sodium and high fat intake; (4) physiologic deviations in human hypertension of such measurables as cardiac output and total peripheral resistance, renal blood flow and resistance, plasma volume, interstitial fluid, blood viscosity, clotting time, adrenal cortical function and the hepatorenal factors demonstrable by the mesoappendix technic; (5) the natural history of the disease in untreated patients, survival rates

of medically and surgically treated patients, and the physician's role in management of these patients.

Also considered were the indications and usefulness of such diverse therapeutic approaches as (1) observation, reassurance and mild sedation, (2) low sodium and rice diets, (3) oral administration of renal extracts and oxidized marine oils, (4) pharmacologic agents: the extracts of veratrum, adrenergic blocking agents, and water soluble pyrogens given intravenously, and (5) the surgical technics of splanchnic and lumbar ganglionectomy, thoracolumbar sympathectomy and interruption of cortical pathways.

The following is the reviewer's report of the essence of the meeting: The problem of hypertensive disease is complex. Many agree that the disturbance often seems hereditary and is manifest in youth or early adult life. Such somatic features as muscularity, love of activity, and obesity are common. Whether or not certain traits of personality are present in all patients remains to be demonstrated. Also questionable is the idea that all hypertensive persons at the onset are involved in situations which make them feel threatened. The foregoing orientation suggests that personality problems may alert the organism by way of cortical pathways to the hypothalamus, the pituitary and the medullary centers. Interruption of certain of these pathways by psychosurgical technics may alter the hypertensive state but they have not consistently reversed it. The anatomic pathways, and the precise contribution of various nervous system levels in the integration of blood pressure regulation in normal, prehypertensive, and hypertensive people have not been defined. Quantitation of the contribution of the pituitary-adrenal, the autonomic nervous system and hepatorenal factors in patients with labile hypertension and with fixed diastolic hypertension is not yet possible. The response of each type of patient to a stressful situation such as an emotional upset, muscular exercise, the upright position, salt restriction and desoxycorticosterone administration is insufficiently documented. The existence of an effector substance, chemical definition of this substance or its antagonists, and the factors influencing the reactivity of blood vessels in hypertensive patients to these humoral agents is an area of great activity, with few indisputable facts as yet available.

The diagnosis of hypertensive vascular disease is difficult because of lack of agreement as to the definition of what constitutes hypertension in the older age groups. There is a difference in the disease course of older patients having the high systolic, wide pulse pressure hypertension and that of the younger patients having a high diastolic pressure. The importance of careful study of the latter patients having diastolic pressures persistently above 120 mm. Hg was stressed. Periodic evaluation of those patients in the attempt to assess the rate of progress of the vascular damage in the brain, retina, heart and kidneys is essential. Periodic repetition of baseline studies of vascular damage enables one to define treatment that is consistent with the severity and the rate of progression of the disease process. "If the disease is malignant and rapidly progressing, heroic measures are demanded." Diet and drugs such as veratrum extracts and chemically distinct compounds (protoveratrine, the phthalazines and hexamethonium) have not yet been shown to produce survival rates in group III (Smithwick) patients comparable with those obtained following dorsolumbar sympathectomy. Group IV patients, making up about 3 per cent of all hypertensive patients in a clinic population, have had their life expectancy extended when compared with similar patients treated medically. Nevertheless about 50 per cent of these surgically treated patients have expired in five years. There is no information to explain why a patient having minimal damage may change to the more rapidly progressive, life-shortening phase. The most prevalent practical concern of the symposium was the need for careful and repeated observation of these patients in assessing the acceleration of the disease process in order to have a baseline for evaluation of therapy.

The book is recommended to everyone engaged in research in essential hypertension. Suggestions of gaps yet to be filled are to be found in many of the presentations.

JOSEPH H. HAFKENSCHIEL

Emotional Factors in Cardiovasular Disease, ed. 2. *Edward Weiss.* American Lecture Series in Circulation, No. 97. Springfield, Ill., Charles C Thomas, 1951. 84 pages, $2.25.

The author, widely known for his interest in psychosomatic problems, has composed a brief, clear-cut, readable summary of the relationship of emotional and physical factors in certain cardiovascular disorders. This monograph should find its widest reception and usefulness among medical students and those practitioners whose experience in such matters is limited.

The symptoms commonly associated with cardiac disease and the various aspects of therapy are well reviewed, with emphasis on important relationships to emotional factors. The clinical features of neurocirculatory asthenia, hypertension, hypotension, and some forms of organic heart disease are similarly treated, with pertinent, concise, well-written illustrative case histories.

The author has chosen to focus attention upon the relation of emotion to disease entities, rather than upon the association of emotion with alterations of cardiovascular physiologic behavior. Expression of general ideas and opinions might have been supplemented more generously by summary and critical analysis of the steadily accumulating body of experimental physiologic and psychologic

data bearing upon the interplay of emotions and cardiovascular function.

More specific definition of the term "anxiety," used frequently in chapter headings and text, would be helpful. The need for brevity in the text detracts from the value of the psychodynamic formulations in the case histories, and allows scant attention to emotional factors in the cardiac arrhythmias, rheumatic valvular disease, myocardial infarction, and congestive heart failure.

The author opens the way to much debate in his discussion of the respective contributions of heredity and of environmental influences to "poor physical endowment" in neurocirculatory asthenia. Looseness of implication and lack of definition are implicit in certain statements: "The heart has been the traditional seat of the emotions"; "The real sources of anxiety are totally unknown to the patient"; "Such persons carry an unusual amount of anxiety in their make-up"; "When organic disease of the heart has been eliminated and when significant arrhythmias have not been demonstrated, one can feel certain that the awareness of the heart action is to be explained psychologically"; "cultivation of an erect philosophy of life" in contrast to an "horizontal philosophy of life." Continued use of the term "cardiac neurosis" is not advisable under any circumstances.

The physician is warned strongly in a negative fashion against any activities that might increase the patient's awareness of his heart; more emphasis could profitably be given to positive ways of dealing therapeutically with the emotional states in the patients that are relevant to such morbid interest.

The last chapter, one half page in length, might have been omitted with advantage.

The reviewer is well aware that the author's general message needs wider dissemination and acceptance at all levels of medical practice and strongly approves of his over-all effort in this immensely worthwhile cause.

JOHN T. FLYNN

Fundamentals of Clinical Fluoroscopy, with Essentials of Roentgen Interpretation. *Charles B. Storch.* New York, Grune & Stratton, 1951. 196 pages, 217 illustrations, $6.75.

This basic text on clinical fluoroscopy is an innovation in that it is written for the clinician rather than the x-ray specialist. The tremendous increase in recent years in the use of the fluoroscope by the internist is in itself justification for the book's existence.

There are six chapters. Chapter I, Basic Concepts: Mechanics, Protection, and Dark Adaptation (10 pages), consists of material which, unfortunately, is too often assumed to be known by the novice. Protection of patient and operator is stressed.

Each of the five remaining chapters covers an organ, or organs, beginning with normal anatomy and special fluoroscopic technic for the particular organ, and ending by describing a representative selection of commonly encountered abnormalities. Chapter II (30 pages) concerns the chest; Chapter III (42 pages) the heart; Chapter IV (24 pages) the pharynx, hypopharynx, and esophagus; and Chapters V and VI (75 pages) the stomach and colon. While only one-fourth of the book is devoted exclusively to an examination of the heart, over one-half concerns closely related subjects.

The reviewer feels that examination of the gastrointestinal tract is not usually within the domain of the clinician, and that the last two chapters, excellent though they are, have no place in this particular volume.

The chapter on the heart begins with a review of the anatomy and projection of the cardiac silhouette in the various positions. The normal heart, including effects of position, respiration, and spinal deformities, is considered. The subject of border pulsations is followed by a study of chamber enlargement. Following a suggested routine for examination, cardiac mensuration, including orthodiascopy, is discussed. The study of the aorta and pulmonary artery is followed by a description of calcification of the pericardium and the valves. The chapter ends with a consideration of pericardial effusion, ventricular aneurysm, thyroid and beriberi heart.

A lucid style supplemented by outstanding illustrations, many of which are original and ingenious teaching aids of the author, make this text a book that should be required reading for anyone preparing for the performance of fluoroscopic examinations. The author's stated purpose is not to make the reader an accomplished fluoroscopist—experience at the side of a trained worker being essential—but to present sufficient background to assist the learning process through an understanding of basic principles plus practical hints, thereby developing an informed and logical approach. In attaining this purpose the book should be highly successful.

A. HENRY CLAGETT, JR.

The Physiology and Pathology of Hemostasis. *Armand J. Quick.* Philadelphia, Lea and Febiger, 1951. 188 pages, $4.00.

This monograph is about equally divided into a clinical part and laboratory methods. These methods and tests are the ones which the author considers most valuable for the clinical study of hemorrhagic diseases. There is emphasis on attention to details in procedure rather than historical background or comparisons with the methods of other investigators. Altogether 21 tests are described.

The clinical section discusses historical developments of the concepts of hemostasis, a new theory of the coagulation of the blood and a unified concept of hemostasis, the classification of the hemorrhagic diseases and their diagnosis, the treatment of the hemorrhagic diseases and their surgical handling,

and venous thrombosis. The clarity of the discussion should make it easy for the student to assimilate the information from cover to cover with the greatest ease. The book is very stimulating, and informative. The author not only avoids conflicting theories and contrary conclusions, but is likely to succeed in leaving the impression that all of his views are based on sound observations and well-controlled experimental evidence.

At one point in the book it is stated that it is not sufficient "to transfer blood to a test tube; one must also carry with it an intuitive feeling for physiological reactions and an insight into the scheme of body function." That viewpoint places this work on a foundation which is not used in very many laboratories. Consequently, the contribution is in a class by itself and cannot be exactly evaluated with conventional standards of judgment. It is quite right to rely on intuition and make a related interpretation but sooner or later someone must furnish the incontrovertible evidence for or against the statement. That takes not only observations of intuition but also of our perceptions in the laboratory. From that viewpoint I find myself repeatedly wanting to ask "What is the evidence" or even to say "This is very likely not correct." This review does not attempt to comment on each point drawing such reaction.

WALTER H. SEEGERS

Diseases in Old Age. A Clinical and Pathological Study of 7,941 Individuals over 61 Years of Age. *Robert T. Monroe.* Harvard University Monographs in Medicine and Public Health. Boston, Harvard University Press, 1951. 407 pages, 92 tables, $5.00.

Here is an important book. It is a survey of 7,941 records of individuals over 61 years of age who have been carefully and thoroughly examined on the Medical Service of the Peter Bent Brigham Hospital, in Boston, since its opening in March 1913.

Following a general discussion bearing on nationalities, age incidence, hospital visits, occupations, marital and economic status and other key data, the discussion concentrates on details of disorders of the nervous system, the cardiovascular system, respiratory system, the gastrointestinal system, the urinary tract, the blood, the endocrines, bones and joints; finally there are chapters on venereal diseases, malnutrition, alcoholism, and tumors.

The summary consists of a resume of the various highlights revealed in the foregoing chapters. There are quotable highlights in abundance in the brilliant consideration of community resources essential for old people, which is the concluding chapter. To mention one or two, Monroe emphasizes the futility of concentrating treatment on any one disorder in older individuals, since as age progresses, there is often an accumulation and interaction of various chronic conditions. He insists that most old people are normal. He points out that very few chronic diseases are progressive of themselves, but may advance due to the accumulative character and inadequate treatment of particular conditions.

Since old age is an integral part of life it can be lived normally and need not all be downgrade. The task of the geriatrician is to discover and provide facilities which will assist oldsters in deriving the most out of the later years.

Of community resources the author discusses medical services with stress on the creation of a geriatric clinic for each hospital. Then follow worthwhile considerations of educational resources, employment, recreation, housing, and finally the creation of an old age center in every large city.

This book is a milestone on the way to a clearer understanding of the medical and social problems of our older citizens.

EDWARD L. BORTZ

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ABSTRACTS IN TRIPLICATE

As previously announced, arrangements have been made for a special session for the presentation of papers dealing with the basic science aspects of cardiovascular disease at the Association's Scientific Sessions, April 18 and 19, at the Hotel Statler in Cleveland. Dr. Irvine H. Page, Chairman of the Program Committee, announces that the deadline date for the receipt of abstracts of such papers has been extended to February 1. Abstracts should be sent **in triplicate** to Dr. Page at the Cleveland Clinic, 2020 East 93rd Street, Cleveland 6, Ohio.

SPECIAL PROGRAM

On the first day of the Association's Annual Scientific Sessions, Friday, April 18, a special program has been scheduled for nonmedical members of the AHA Assembly, national delegate body, and other laymen attending the Annual Meeting. In the morning, reports and demonstrations of research, education, and community service activities of heart associations will be presented. In the afternoon, a round-table discussion has been scheduled between physicians and members of the press, with questions from the audience.

1952 HEART FUND

Bruce Barton will serve once again as National Chairman of the Heart Fund drive. He will hold that position for the second successive year when the Association conducts its fund-raising campaign throughout the month of February. Mr. Barton is Chairman of the Board of the advertising agency, Batten, Barton, Durstine & Osborn, Inc.

The campaign slogan, "New Hope for Hearts," has been retained to stress the scientific advances being made against cardiovascular diseases. American Heart Week, including St. Valentine's Day, has been set for February 10–16.

Other national campaign officers include: Charles E. Wilson, President, General Motors Corporation, Campaign Vice-Chairman; Winthrop W. Aldrich, Chairman of the Board, Chase National Bank, National Campaign Treasurer; Hon. Jesse M. Donaldson, U. S. Postmaster General, Chairman of Federal Employees Committee; Hon. Maurice J. Tobin, U. S. Secretary of Labor, Chairman of Labor Committee; Thomas M. McDonnell, Director of Radio, Foote, Cone and Belding, Chairman of Radio Committee; and Rodney Erickson, Manager of Radio and TV Department, Young & Rubicam, Inc., Chairman of Television Committee.

INTERAMERICAN CONGRESS

The Fourth Interamerican Cardiological Congress will be held in Buenos Aires, Argentina, August 31 to September 6, 1952. Dr. Pedro Cossio of Argentina will preside. Arrangements are being made to reduce the cost of transportation and lodging. A 50 per cent reduction in round-trip fare to Argentina is expected to be granted by the Argentine Air Lines and the Argentine Merchant Fleet to those attending the conference.

CLINIC COMMITTEE'S MEETING POSTPONED

The special meeting of the entire Committee on Cardiovascular Clinics, originally scheduled for January 26 in Chicago at the Palmer House, has been postponed to February 21, 1952.